A NOVEL APPROACH TO ACCELERATE THE DISSOLUTION OF ENTERIC POLYMER COATINGS

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This thesis describes research conducted in the School of Pharmacy, University of London between 2004 and 2007 under the supervision of Dr Abdul W. Basit. I certify that the research described is original and that any parts of the work that have been conducted by collaboration are clearly indicated. I also certify that I have written all text herein and have clearly indicated by suitable citation any part of this dissertation that has already appeared in publication.

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ABSTRACT

Enteric-coated products dissolve rapidly *in vitro* in simulated intestinal conditions, but *in vivo* these products can take up to 2 hours to disintegrate in the human small intestine. A variety of approaches were investigated in this study to accelerate the dissolution of conventional enteric coatings in conditions resembling the upper small intestine. pH-sensitive materials (organic acids and swelling polymers) were incorporated into enteric polymer films based on methacrylic acid ethyl acrylate copolymer – Eudragit® L 30 D-55 (aqueous) and Eudragit® L 100-55 (organic). Both the organic acids and pH-sensitive polymers leached out from the film in pH 1.2 HCl and were not able to accelerate the film dissolution in subsequent buffer.

A novel double-coated system was designed based on the film study with organic acids. The system comprises an inner coat of partially neutralized Eudragit® L 30 D-55 and organic acid, and an outer coat of normal Eudragit® L 30 D-55 coating, applied to a solid core. Prednisolone tablets were coated with the double coating formulations and exhibited good acid resistance. Drug release was substantially accelerated from the double-coated tablets compared to the single layer Eudragit® L 30 D-55 coated (control-coated) tablets in subsequent pH 5.6 phosphate buffer. The drug release lag times for the double-coated and the control-coated tablets were 5 and 100 minutes respectively in buffer. The rapid drug release from the double coating was associated with the faster polymer dissolution velocities measured, compared to the control coating. Confocal laser scanning microscopy revealed that the inner coat of the double coating dissolved before the outer coat and assisted the dissolution of the outer coat.

The inner coat ionic strength and buffer capacity contribute independently to the acceleration of the outer coat dissolution and corresponding drug release from the double-coated system. This was associated with the migration of ions from the inner to the outer coat during dissolution process, as illustrated by energy dispersive X-ray spectroscopy testing, using sodium as a representative ion. The novel double-coated system offers a means to provide fast drug release in the small intestine and overcome the limitations of conventional enteric coatings.
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CHAPTER 1. INTRODUCTION

1.1 Overview

1.2 GASTROINTESTINAL PHYSIOLOGY AND ITS RELEVANCES TO THE IN VIVO PERFORMANCE OF ENTERIC COATINGS

1.2.1 Overview of the GI tract

1.2.2 pH in the GI tract

1.2.2.1 Gastric pH

1.2.2.2 pH in the small intestine and colon

1.2.3 GI transit

1.2.3.1 Gastric emptying

1.2.3.2 Small intestinal transit time

1.2.4 Electrolytes secretion in GI tract

1.2.4.1 Electrolytes in gastric secretion
1.2.4.2 Electrolytes in intestinal secretion ..............................................................26

1.3 MATERIALS USED FOR ENTERIC COATINGS .................................................26

1.3.1 Historical development of enteric coating materials .........................................26

1.3.2 Cellulose-based polymers and polyvinyl derivatives ........................................28

1.3.2.1 Cellulose-based enteric polymers .................................................................28

1.3.2.2 Polyvinyl derivatives .....................................................................................30

1.3.2.3 Factors influencing the solubility of cellulose-based enteric polymers and polyvinyl derivatives ............................................................................................30

1.3.3 Polymethacrylates .............................................................................................32

1.3.4 Comparison of different enteric coatings ...........................................................34

1.4 IN VIVO/IN VITRO EVALUATION OF ENTERIC COATINGS .......................37

1.4.1 In vivo methods ..................................................................................................37

1.4.2 In vitro methods ..................................................................................................38

1.4.2.1 Disintegration test ............................................................................................38

1.4.2.2 Dissolution test ...............................................................................................39

1.4.2.3 Similarity of the in vitro methods and vivo conditions ..................................40

1.5 IN VITRO/IN VIVO DISCREPANCY OF ENTERIC COATING PERFORMANCE .......................................................................................................43

1.6 CLINICAL IMPLICATIONS OF DELAYED DRUG RELEASE FROM ENTERIC-COATED DOSAGE FORMS ...........................................................46

1.7 POTENTIAL STRATEGIES FOR ACCELERATING THE DISSOLUTION OF CONVENTIONAL ENTERIC COATINGS .........................................................49

1.7.1 Chemical approaches ..........................................................................................49
CHAPTER 2. EFFECTS OF pH-SENSITIVE MATERIALS ON ENTERIC POLYMER FILM DISSOLUTION

2.1 INTRODUCTION

2.1.1 The use of pH-sensitive materials for accelerating enteric coating dissolution

2.1.2 The use of free films for investigating coating formulations

2.1.2.1 Mechanisms of film formation

2.1.2.2 Cast vs sprayed films

2.1.3 Model enteric coatings used in the study

SECTION 1: THE USE OF ORGANIC ACIDS IN ENTERIC POLYMER FILMS

2.2 INTRODUCTION

2.3 MATERIALS

2.4 METHODS

2.4.1 Preparation of acid and buffer solutions

2.4.2 Solubility of organic acids

2.4.3 Preparation of polymeric films
2.8 METHODS ................................................................................................................104
2.8.1 Preparation of polymeric films ...........................................................................104
2.8.1.1 Preparation of pure pH-sensitive polymer films .............................................104
2.8.1.2 Preparation of pH-sensitive polymer-containing Eudragit® L 30 D-55
   films .....................................................................................................................105
2.8.2 Acid/buffer uptake and weight loss testing of films ........................................106
2.8.3 Determination of sodium concentration in the films .......................................106
2.9 RESULTS AND DISCUSSION ............................................................................107
2.9.1 Dissolution properties of pure pH-sensitive polymer films .........................107
2.9.2 The inclusion of pH-sensitive polymers in Eudragit® L 30 D-55 films ......111
   2.9.2.1 Pectin and xanthan gum .............................................................................111
   2.9.2.2 Sodium alginate .........................................................................................115
2.10 CONCLUSION .....................................................................................................120

CHAPTER 3. POTENTIAL FOR A DOUBLE-COATED SYSTEM TO ACCELERATE THE DISSOLUTION OF ENTERIC COATINGS.................................................................122
3.1 INTRODUCTION....................................................................................................123

SECTION 1: IN VITRO DRUG RELEASE FROM DOUBLE-COATED PREDNISOLONE TABLETS........................................................................................................127
3.2 INTRODUCTION....................................................................................................127
3.3 MATERIALS ............................................................................................................128
3.4 METHODS ..............................................................................................................130

3.4.1 Preparation of prednisolone tablets.....................................................................130

3.4.2 Coating of prednisolone tablets with Eudragit® L 30 D-55 formulations... 130

3.4.2.1 Preparation of coating dispersions.................................................................131

3.4.2.2 Film coating for prednisolone tablets ..............................................................132

3.4.3 Scanning electron microscopy..............................................................................134

3.4.4 In vitro drug release testing .................................................................................134

3.5 RESULTS AND DISCUSSION ............................................................................135

3.5.1 Scanning electron micrographs of the control-coated and the double-coated
tablets......................................................................................................................135

3.5.2 Acid-resistance tests .............................................................................................137

3.5.3 Comparison of drug release from the double-coated and the control-coated
prednisolone tablets in different buffer pH.............................................................138

SECTION 2: POLYMER DISSOLUTION VELOCITY TESTS

USING GLASS BEADS............................................................................................144

3.6 INTRODUCTION...................................................................................................144

3.7 MATERIALS............................................................................................................146

3.8 METHODS...............................................................................................................146

3.8.1 Coating of glass beads with Eudragit® L 30 D-55 formulations ..............146

3.8.1.1 Preparation of coating dispersions.................................................................146

3.8.1.2 Film coating for glass beads............................................................................147

3.8.2 Polymer dissolution velocity tests on coated glass beads.........................148
3.8.2.1 Testing process ....................................................................................................148
3.8.2.2 Calibration curve for RI-detector .................................................................150
3.8.2.3 Calculation of polymer dissolution velocities .................................................150
3.9 RESULTS AND DISCUSSION ................................................................................151
3.9.1 Comparison of polymer dissolution velocities from the control-coated and the double-coated glass beads in different buffer pH ............................................151
3.9.2 Correlation of polymer dissolution velocities to drug release results ............154

SECTION 3: COATING DISSOLUTION PROCESS USING CONFOCAL LASER SCANNING MICROSCOPY .................................................................................................156
3.10 INTRODUCTION ..................................................................................................156
3.11 MATERIALS .........................................................................................................158
3.12 METHODS .............................................................................................................159
3.12.1 Preparation of prednisolone pellets .................................................................159
3.12.2 Coating of prednisolone pellets with Eudragit® L 30 D-55 formulations ...159
3.12.2.1 Preparation of coating dispersions or solutions ............................................159
3.12.2.2 Film coating for prednisolone pellets ...........................................................160
3.12.3 In vitro drug release testing for coated prednisolone pellets ......................161
3.12.4 Confocal Laser Scanning Microscopy testing ...............................................161
3.12.4.1 Dissolution of coated pellets for confocal testing .......................................161
3.12.4.2 Confocal testing ............................................................................................162
3.13 RESULTS AND DISCUSSION .............................................................................163
SECTION 4: OPTIMIZATION OF THE DOUBLE COATING SYSTEM

3.14 INTRODUCTION............................................................................................................ 169
3.15 MATERIALS...................................................................................................................... 171
3.16 METHODS....................................................................................................................... 171
3.16.1 Coating of prednisolone tablets................................................................................ 171
3.16.2 In vitro drug release testing....................................................................................... 173
3.16.3 Acid uptake by tablets............................................................................................... 174
3.16.4 Scanning electron microscopy................................................................................... 175
3.16.5 Differential scanning calorimetry............................................................................... 175
3.17 RESULTS AND DISCUSSION....................................................................................... 176
3.17.1 Influence of species and concentration of organic acid in the inner coat on drug release ............................................................................................................................ 176
3.17.2 Influence of outer coat thickness on drug release.................................................... 179
3.17.3 Influence of the neutralization value of the inner coat on drug release................. 185
3.18 CONCLUSION................................................................................................................ 190

CHAPTER 4. UNDERSTANDING THE MECHANISMS INVOLVED IN THE DISSOLUTION OF THE DOUBLE COATING SYSTEM .................................................................................................................. 192
4.1 INTRODUCTION............................................................................................................ 193
4.2 MATERIALS...................................................................................................................... 194
4.3 METHODS....................................................................................................................... 195
4.3.1 Comparison studies

4.3.1.1 Coating of prednisolone tablets

4.3.1.2 In vitro drug release testing

4.3.2 Influence of ionic strength and buffer capacity on the double coating dissolution

4.3.2.1 Ionic strength

4.3.2.2 Buffer capacity

4.3.3 Migration of sodium ions from the inner to the outer coat of the double coating system

4.3.3.1 Preparation of samples

4.3.3.2 Determination using scanning electron microscopy/energy dispersive X-ray spectroscopy (SEM/EDX)

4.3.4 Influence of inner coat osmotic pressure on drug release from double-coated formulations

4.3.4.1 Determination of acid and buffer uptake of the double-coated system

4.3.4.2 Influence of osmotic pressure on drug release

4.4 RESULTS AND DISCUSSION

4.4.1 Comparison studies

4.4.1.1 Inner coat with organic acid but without neutralization

4.4.1.2 Inner coat with neutralization but without organic acid

4.4.1.3 Comparison with hypromellose (HPMC) as sub-coat

4.4.2 The roles of inner coat ionic strength and buffer capacity on the double coating
dissolution..............................................................................................................214

4.4.2.1 Influence of salts and acids on the dissolution of Eudragit® L 30 D-55
polymer..................................................................................................................214

4.4.2.2 Calculation of the ionic strength and buffer capacity of the inner coat
formulations ...........................................................................................................218

4.4.2.3 The roles of inner coat ionic strength and buffer capacity on the dissolution
of the double-coated system..............................................................................222

4.4.3 Migration of sodium ions from the inner to the outer coat during dissolution
process..................................................................................................................227

4.4.4 The role of inner coat osmotic pressure on drug release from the double-coated
system ..................................................................................................................232

4.4.4.1 Determination of inner coat osmotic pressure.................................232

4.4.4.2 Influence of osmotic pressure on drug release.................................234

4.4.5 General discussion of the dissolution mechanism of the double-coated
system..................................................................................................................238

4.5 CONCLUSION.....................................................................................................241

CHAPTER 5. GENERAL DISCUSSION AND FUTURE WORK.............................................242

5.1 GENERAL DISCUSSION AND CONCLUSIONS.............................................243

5.2 FUTURE WORK.................................................................................................248
LIST OF FIGURES

CHAPTER ONE

Figure 1.1.  Diagram of the human gastrointestinal tract...............................8
Figure 1.2.  Gastrointestinal pH profile from a normal subject .......................10
Figure 1.3.  Location of the duodenal bulb.....................................................14
Figure 1.4.  The structure of a substituted cellulose.  (R can be represented as —H or,
different substituent groups depending on the individual polymer)..................28
Figure 1.5.  Chemical structure of PVAP. Depending on the phthalyl content, a will
vary with b in mole percent. The acetyl content c remains constant depending on the
starting material.................................................................................................30
Figure 1.6.  Mean (SD) plasma concentration-time profiles for didanosine obtained
after administration of the buffered tablet (●), enteric beads (▲), and enteric tablet (■)
formulations to healthy male volunteers (n=18).............................................49

CHAPTER TWO

Figure 2.1.  Mechanism of film formation from aqueous dispersion...............60
Figure 2.2.  Particle coalescence during the evaporative phase......................61
Figure 2.3.  Typical EDX spectrum .................................................................75
Figure 2.4.  Acid uptake (a) and weight loss (b) as functions of time for Eudragit®
L 100-55 films with TEC or organic acids in pH 1.2 HCl ..................................78
Figure 2.5.  Scanning electron micrographs of the surfaces of Eudragit® L 100-55
films....................................................................................................................79
Figure 2.6.  Buffer uptake (a) and weight loss (b) as functions of time for Eudragit®
L 100-55 films with TEC or organic acids in pH 6.2 phosphate buffer.............81
Figure 2.7. DSC thermogram of Eudragit® L 100-55 film with 10% TEC.................83

Figure 2.8. Acid uptake (a) and weight loss (b) as functions of time for Eudragit® L 100-55 films with TEC and organic acids in pH 1.2 HCl.................................85

Figure 2.9. Buffer uptake (a) and weight loss (b) as functions of time for Eudragit® L 100-55 films with TEC and organic acid in pH 6.2 phosphate buffer..........................................................................................87

Figure 2.10. Acid uptake (a) and weight loss (b) as functions of time for Eudragit® L 30 D-55 films with TEC and organic acids in pH 1.2 HCl.................................89

Figure 2.11. Buffer uptake (a) and weight loss (b) as functions of time for Eudragit® L 30 D-55 films with TEC and organic acid in pH 6.0 phosphate buffer..........................................................................................91

Figure 2.12. Acid uptake (a) and weight loss (b) as functions of time for Eudragit® L 30 D-55 films with TEC and adipic acid in pH 1.2 HCl.................................93

Figure 2.13. Buffer uptake (a) and weight loss (b) as functions of time for Eudragit® L 30 D-55 films with TEC and adipic acid in subsequent pH 6.0 phosphate buffer after in pH 1.2 HCl for 2 hours .........................................................94

Figure 2.14. Chemical structure of pectin .................................................................99

Figure 2.15. Structural characteristics of alginates: (a) alginate monomers, (b) chain conformation, (c) block distribution.................................................................100

Figure 2.16. Chemical structure of xanthan...............................................................101

Figure 2.17. Acid uptake (a) and weight loss (b) of pure alginates films and Eudragit® L 30 D-55 film in pH 1.2 HCl.................................................................109

Figure 2.18. Buffer uptake (a) and weight loss (b) of pure alginates films and Eudragit® L 30 D-55 film in subsequent pH 5.8 phosphate buffer after 2 hours in pH 1.2 HCl..............................................................................................110

Figure 2.19. Acid uptake (a) and weight loss (b) of Eudragit® L 30D-55 film with different concentration of pectin and TEC in pH 1.2 HCl.................................112

Figure 2.20. Buffer uptake (a) and weight loss (b) of Eudragit® L 30 D-55 film with different concentrations of pectin and TEC in subsequent pH 5.8 phosphate buffer after 2 hours in pH 1.2 HCl..............................................................................................113
Figure 2.21. Film formation process from pectin-containing Eudragit® L 30 D-55 dispersion

Figure 2.22. Acid uptake (a) and weight loss (b) of Eudragit® L 30 D-55 film with sodium alginate in pH 1.2 HCl

Figure 2.23. Buffer uptake (a) and weight loss (b) of Eudragit® L 30 D-55 film with sodium alginate in subsequent pH 5.8 phosphate buffer after 2 hours in pH 1.2 HCl

Figure 2.24. Sodium and carbon distribution in the cross-section of 50% sodium alginate-containing Eudragit® L 30 D-55 film

Figure 2.25. Scanning electron micrographs of the cross-section of the pure sodium alginate film and the 50% sodium alginate-containing Eudragit® L 30 D-55 film

CHAPTER THREE

Figure 3.1. Demonstration of the normal single-layer enteric coating (Eudragit® L 30 D-55 was used as an example)

Figure 3.2. Demonstration of the double coating system

Figure 3.3. Chemical structure of prednisolone

Figure 3.4. Scanning electron micrographs of the surface and cross-section of the control-coated and the double-coated tablets

Figure 3.5. Drug release profiles of the Eudragit® L 30 D-55 double-coated and the control-coated prednisolone tablets in pH 5.0 phosphate buffer after pre-treatment in pH 1.2 HC for 2 hours

Figure 3.6. Drug release profiles of the Eudragit® L 30 D-55 double-coated and the control-coated prednisolone tablets in pH 5.5 phosphate buffer after pre-treatment in pH 1.2 HCl for 2 hours

Figure 3.7. Drug release profiles of the Eudragit® L 30 D-55 double-coated and the control-coated prednisolone tablets in pH 5.6 phosphate buffer after pre-treatment in pH 1.2 HCl for 2 hours

Figure 3.8. Drug release profiles of the Eudragit® L 30 D-55 double-coated and the control-coated prednisolone tablets in pH 5.8 phosphate buffer after pre-treatment in
pH 1.2 HCl for 2 hours. .................................................................140

**Figure 3.9.** Drug release profiles of the Eudragit® L 30 D-55 double-coated and the control-coated prednisolone tablets in pH 6.0 phosphate buffer after pre-treatment in pH 1.2 HCl for 2 hours. .............................................................................................................140

**Figure 3.10.** Drug release profiles of the Eudragit® L 30 D-55 double-coated and the control-coated prednisolone tablets in pH 6.2 phosphate buffer after pre-treatment in pH 1.2 HCl for 2 hours. .............................................................................................................141

**Figure 3.11.** Schematic picture of the apparatus for measuring the polymer dissolution velocities .................................................................................................................149

**Figure 3.12.** Comparison of polymer dissolution velocities from the double-coated and the control-coated glass beads at different buffer pH, after 2 hours pre-treatment in pH 1.2 HCl.................................................................152

**Figure 3.13.** Comparison of polymer dissolution velocities from the double-coated and the control-coated glass beads at pH 5.5 with and without acid pre-treatment .............................................................................................................153

**Figure 3.14.** Demonstration of theoretical principle of CLSM..............................157

**Figure 3.15.** The net device used for pellet dissolution testing. .........................162

**Figure 3.16.** Confocal images of the double-coated and the control-coated pellets before and after 2 hours treatment in pH 1.2 HCl.............................................................................................................163

**Figure 3.17.** Confocal images of the control-coated pellets at different time points in pH 5.5 phosphate buffer .................................................................................................164

**Figure 3.18.** Confocal images of the double-coated pellets at different time points in pH 5.5 phosphate buffer .................................................................................................166

**Figure 3.19.** Drug release profiles of the Eudragit® L 30 D-55 double-coated, the control-coated and the HPMC sub-coated prednisolone pellets in pH 5.5 phosphate buffer after pre-treatment in pH 1.2 HCl for 2 hours ..................................................................................168

**Figure 3.20.** Scanning electron micrographs of the surface of different inner coats of the double-coated prednisolone tablets ..................................................................................177

**Figure 3.21.** Tₜ values of Eudragit® L 30 D-55 films (neutralized to pH 5.6) with different adipic acid and citric acid concentrations ..................................................................................179
Figure 3.22. Drug release profiles of the control-coated prednisolone tablets with different coat thicknesses in pH 5.6 phosphate buffer after pre-treatment in pH 1.2 HCl for 2 hours ............................................................................................................................180

Figure 3.23. Drug release profiles of the Eudragit® L 30 D-55 double-coated prednisolone tablets (10% citric acid in the inner coat) with different outer coat thicknesses in pH 5.6 phosphate buffer after pre-treatment in pH 1.2 HCl for 2 hours ............................................................................................................................182

Figure 3.24. Drug release profiles of the Eudragit® L 30 D-5 double-coated prednisolone tablets (10% adipic acid in the inner coat) with different outer coat thicknesses in pH 5.6 phosphate buffer after pre-treatment in pH 1.2 HCl for 2 hours ............................................................................................................................182

Figure 3.25. Drug release profiles of the Eudragit® L 30 D-55 double-coated prednisolone tablets (10% citric acid in the inner coat) with different inner coat pH values in pH 5.6 phosphate buffer after pre-treatment in pH 1.2 HCl for 2 hours ............................................................................................................................186

Figure 3.26. Drug release profiles of the Eudragit® L 30 D-55 double-coated and the control-coated prednisolone tablets in pH 6.8 sodium phosphate buffer after pre-treatment in pH 1.2 HCl for 2 hours ............................................................................................................................189

Figure 3.27. Drug release profiles of the Eudragit® L 30 D-55 double-coated and the control-coated prednisolone tablets in pH 7.4 Hanks buffer after pre-treatment in pH 1.2 HCl for 2 hours ............................................................................................................................189

Figure 3.28. Drug release profiles of the Eudragit® L 30 D-55 double-coated and the control-coated prednisolone tablets in pH 6.8 Hanks/MES buffer after pre-treatment in pH 1.2 HCl for 2 hours ............................................................................................................................190

CHAPTER FOUR

Figure 4.1. SEM picture of the cross-section of the double-coated pellets and the division of the coat into sections ............................................................................................................................200

Figure 4.2. Drug release profiles of Eudragit® L 30D-55 double-coated prednisolone tablets with organic acid in the inner coat but without neutralization, in pH 5.6 phosphate buffer after 2 hours in pH 1.2 HCl ............................................................................................................................204

Figure 4.3. Comparison of drug release profiles of Eudragit® L 30D-55 double-coated prednisolone tablets with and without citric acid in the inner coat in pH 5.6 phosphate
buffer after 2 hours in pH 1.2 HCl .................................................................206

Figure 4.4. Comparison of drug release profiles of the Eudragit® L 30 D-55 control-coated prednisolone tablets with the HPMC sub-coated tablets in pH 5.6 phosphate buffer after pre-treatment in pH 1.2 HCl for 2 hours .........................208

Figure 4.5. Confocal images of the HPMC sub-coated pellets before and after 2 hours in pH 1.2 HCl .................................................................209

Figure 4.6. Confocal images of the HPMC sub-coated pellets in pH 5.5 phosphate buffer after 2 hours in pH 1.2 HCl .................................................................210

Figure 4.7. Comparison of drug release profiles of the Eudragit® L 30 D-55 double-coated prednisolone tablets with the HPMC sub-coated tablets in pH 5.6 phosphate buffer after pre-treatment in pH 1.2 HCl for 2 hours .................................................................212

Figure 4.8. Titration curves of Eudragit® L 30 D-55 with and without sodium citrate .........................................................................................215

Figure 4.9. Neutralization curves of Eudragit® L 30 D-55 with and without sodium citrate .........................................................................................216

Figure 4.10. Neutralization curves of Eudragit® L 30 D-55 with different organic acids using the volume of 1 M NaOH consumed .........................................................................................217

Figure 4.11. Comparison of drug release profiles of the Eudragit® L 30 D-55 double-coated prednisolone tablets with 10% citric acid, sodium citrate or adipic acid in the inner coat in pH 5.6 phosphate buffer after pre-treatment in pH 1.2 HCl for 2 hours .........................................................................................226

Figure 4.12. Scanning electron micrographs of the double-coated pellets at different time points in pH 5.5 phosphate buffer .........................................................................................228

Figure 4.13. EDX images of sodium ions distribution in the cross-section of the double-coated pellets after removal from pH 5.5 phosphate buffer at different time points .........................................................................................230

Figure 4.14. The concentration of sodium ions in different sections of the coat of the double-coated pellets after removal from pH 5.5 phosphate buffer at different time points .........................................................................................231

Figure 4.15. Drug release profiles of the Eudragit® L 30 D-55 double-coated prednisolone tablets with 10% citric acid in the inner coat in pH 5.6 phosphate buffer with different urea concentrations after pre-treatment in pH 1.2 HCl for 2
Figure 4.16. Drug release profiles of the Eudragit® L 30 D-55 double-coated prednisolone tablets with 10% adipic acid in the inner coat in pH 5.6 phosphate buffer with different urea concentrations after pre-treatment in pH 1.2 HCl for 2 hours.

Figure 4.17. The weight change of the coat of the Eudragit® L 30D-55 control-coated and double-coated glass beads in pH 5.6 phosphate buffer after 2 hours in pH 1.2 HCl.

Figure 4.18. Schematic definition of the dissolution process of the outer coat of the double-coated system; the initial physical film thickness, \( l_o \), the thickness of film with migrated acids and salts, \( l_m \), the thickness of film dissolved from outside, \( l_{d1} \), the thickness of film dissolved from inside, \( l_{d2} \), and the instantaneous physical film thickness, \( l_f \).
CHAPTER ONE

Table 1.1. Medicines available as enteric-coated products in the UK (2007)...........5
Table 1.2. Gastric pH after different meals.................................................................12
Table 1.3. Luminal pH values of the duodenum and jejunum in healthy humans....14
Table 1.4. Concentration of electrolytes in gastric juice (mmol/l).......................25
Table 1.5. Concentration of electrolytes in gastric juice in patients with GI disease (mmol/l, means±SEM).................................................................25
Table 1.6. Concentration of electrolytes in intestinal juice.................................26
Table 1.7. Chemical structures and soluble pH values of some cellulose-based enteric polymers..............................................................29
Table 1.8. Chemical structure and solubility of methacrylic acid copolymers........33
Table 1.9. In vitro and in vivo disintegration time of some enteric-coated dosage forms.................................................................45

CHAPTER TWO

Table 2.1. Some fundamental information of Eudragit® L 30 D-55/L 100-55......63
Table 2.2. Chemical formulation, pKₐ and molecular weight of organic acid......65
Table 2.3. Solubility of organic acids.................................................................77
Table 2.4. Tg values as attained by DSC of Eudragit® L 100-55 powder and films with TEC and organic acids..........................................................83
Table 2.5. Sodium concentration in partially neutralized Eudragit® L 30 D-55 films before and after acid treatment...........................................................................................96

Table 2.6. Sodium concentration in films before and after acid treatment........119

CHAPTER THREE

Table 3.1. Coating conditions of different coating formulations for tablets........132

Table 3.2. Formula for different pH of phosphate buffer.................................135

Table 3.3. Coating conditions of different coating formulations for glass beads .........................................................................................................................147

Table 3.4. Coating conditions for prednisolone pellets.................................160

Table 3.5. Double coating formulations for prednisolone tablets....................172

Table 3.6. Formula for pH 7.4 Hanks buffer......................................................174

Table 3.7. Drug release from the double-coated prednisolone tablets with different species and concentrations of organic acids in the inner coat in pH 5.6 buffer after 2 hours in pH 1.2 HCl.............................................................176

Table 3.8. Acid uptake of the control-coated prednisolone tablets.................183

Table 3.9. Acid uptake of the 10% adipic acid double-coated prednisolone tablets.................................................................................................................................183

Table 3.10. Electrolyte composition of intestinal fluids, physiological and phosphate buffers.........................................................................................................................187

CHAPTER FOUR

Table 4.1. Coating conditions of different coating formulations.........................196

Table 4.2. Pkᵣ values and percentage neutralization of Eudragit® L 30 D-55 polymer and organic acids at the pH where complete polymer dissolution occurred........221

Table 4.3. Ionic strength and buffer capacities of different inner coat formulations at
Table 4.4. Acid uptake of the 10% citric acid double-coated and the control-coat glass beads after 2 hours in acid.

Table 4.5. Osmotic pressure of pH 5.6 phosphate buffer with different urea concentrations and the osmotic pressure difference of the inner coat and dissolution media (mosmo/Kg H$_2$O).
**LIST OF ABBREVIATIONS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ac-di-sol</td>
<td>sodium carboxymethylcellulose</td>
</tr>
<tr>
<td>BP</td>
<td>British Pharmacopoeia</td>
</tr>
<tr>
<td>CAP</td>
<td>cellulose acetate phthalate</td>
</tr>
<tr>
<td>CAT</td>
<td>cellulose acetate trimellitate</td>
</tr>
<tr>
<td>CLSM</td>
<td>confocal laser scanning microscopy</td>
</tr>
<tr>
<td>C_{max}</td>
<td>peak plasma concentration</td>
</tr>
<tr>
<td>DSC</td>
<td>differential scanning calorimetry</td>
</tr>
<tr>
<td>EDX</td>
<td>energy dispersive X-ray spectroscopy</td>
</tr>
<tr>
<td>GI</td>
<td>gastrointestinal tract</td>
</tr>
<tr>
<td>HPMC</td>
<td>hypromellose</td>
</tr>
<tr>
<td>HPMCAS</td>
<td>hypromellose acetate succinate</td>
</tr>
<tr>
<td>HPMCP</td>
<td>hypromellose phthalate</td>
</tr>
<tr>
<td>ICJ</td>
<td>ileo-caecal junction</td>
</tr>
<tr>
<td>MES</td>
<td>2-(N-morpholino)ethanesulfonic acid</td>
</tr>
<tr>
<td>MMC</td>
<td>migrating motor complex</td>
</tr>
<tr>
<td>pK_{a}</td>
<td>negative logarithm of the ionisation constant</td>
</tr>
<tr>
<td>PVAP</td>
<td>polyvinyl acetate phthalate</td>
</tr>
<tr>
<td>PVP</td>
<td>polyvinylpyrrolidone</td>
</tr>
<tr>
<td>RI</td>
<td>refractive index</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>SD</td>
<td>standard deviation</td>
</tr>
<tr>
<td>SEM</td>
<td>scanning electron microscopy</td>
</tr>
<tr>
<td>TEC</td>
<td>triethyl citrate</td>
</tr>
<tr>
<td>TIM</td>
<td>dynamic artificial gastrointestinal systems</td>
</tr>
<tr>
<td>$T_g$</td>
<td>glass transition temperature</td>
</tr>
<tr>
<td>$T_{max}$</td>
<td>the time to reach peak plasma concentration</td>
</tr>
<tr>
<td>USP</td>
<td>United States Pharmacopoeia</td>
</tr>
</tbody>
</table>
CHAPTER 1

INTRODUCTION
1.1 OVERVIEW

The preferred and most commonly used route for drug delivery is still the gastrointestinal (GI) tract by oral administration. Traditional immediate release dosage forms release drug in the stomach, ideally providing rapid absorption. In some instances, modified release systems targeting drugs to particular sections of the GI tract may be more beneficial, due to the optimization of drug absorption, treatment of local diseases or reduction of side-effects. Extended release systems and colonic delivery systems have received intensive attention in this field. However, the most common type of modified release preparation is the enteric-coated formulation for targeting to the small intestine.

Enteric coatings exploit the pH differential in the upper GI tract to deliver drugs to the small intestine. Despite the long history and widespread use, little attention has been given to the in vitro/in vivo discrepancy of enteric coating performance. Enteric-coated products dissolve rapidly in vitro in simulated intestinal conditions. Therefore there is a common misconception that enteric-coated products disintegrate rapidly after emptying from the stomach. In vivo such products can take up to 2 hours to disintegrate in the human small intestine. Such a lack of consistency of the in vitro/in vivo performance is attributed to the inadequacy of in vitro dissolution methods to resemble the in vivo small intestinal conditions.

The substantial time delay for conventional enteric coatings to release the active substances in the small intestine has clinical implications. This is especially significant for drugs that have an absorption window in the proximal small intestine or when a rapid onset of action is required. Hence, there is a clear need to achieve rapid drug release from enteric-coated products in the small intestine. The objective of the present study is to accelerate the dissolution of conventional enteric coatings and achieve rapid drug release in conditions resembling the upper small intestine. It is also a concern of the study to achieve a fundamental understanding of the
mechanisms involved in the dissolution of both traditional and novel enteric coating formulations.

1.2 GASTROINTESTINAL PHYSIOLOGY AND ITS RELEVANCES TO
THE IN VIVO PERFORMANCE OF ENTERIC COATINGS

Enteric coatings have been of scientific and commercial interest for more than one century. Such coatings can be applied to a number of pharmaceutical dosage forms, including large single-unit dosage forms such as tablets and capsules, and multi-unit dosage forms such as granules and pellets (Lehmann and Dreher, 1981; Murthy et al., 1986; Schmidt and Niemann, 1992; Felton et al., 1995).

Enteric coatings are normally used for three main purposes: (i) to prevent the degradation of active substance by the acidic juice in the stomach, (ii) to protect the stomach from irritating active compounds and, (iii) to target drugs to a specific site of the intestine for treatment of local diseases. Examples of medicaments that are susceptible to degradation by gastric juice include pancreatic enzymes for treatment of pancreatic insufficiency (Lemier and Iber, 1965; Guarner et al., 1993), proton pump inhibitors such as omeprazole, which degrade rapidly in acidic aqueous solutions (Mathew et al., 1995), and antibiotic compounds such as erythromycin, which is transformed from stearate salt into the less active hydrochloride in the stomach (Boggiano and Gleeson, 1976).

Several active substances are widely known to cause irritation of the gastric mucosa, thus resulting in gastric disorders and low tolerance. The nonsteroidal anti-inflammatory drugs such as aspirin, diclofenac and indomethacin have received most attention regarding this problem. The tolerance of these drugs is improved by applying enteric coatings (Rainsford et al., 1981; Petroski, 1989; Bakshi et al., 1993).
Conventionally, enteric coatings are also used to release actives to the small intestine for treatment of small bowel disorders. However, recently great interest has focused on targeting drugs to the colonic region for pharmacotherapy of local diseases including ulcerative colitis and Crohn's disease (Basit, 2005).

A list of medicines available as enteric-coated preparations in the UK is provided in Table 1.1.

Some traditional enteric coatings depend on enzyme break down in the small intestine for release of the active materials. However most currently used enteric coatings rely on the pH differences between the stomach and intestine for their performance. Such coatings based on pH-dependent polymers normally dissolve at pH 5 and above. Understanding the fate and functionality of enteric-coated dosage forms in the GI tract requires a detailed knowledge of GI physiology.
### Table 1.1. Medicines available as enteric-coated products in the UK (2007).

<table>
<thead>
<tr>
<th>Chemical name</th>
<th>Brand names</th>
<th>Dose</th>
<th>Indications</th>
<th>Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acamprosate calcium</td>
<td>Campral®</td>
<td>333 mg</td>
<td>Maintenance of abstinence in alcohol dependence</td>
<td>E/C tablets</td>
</tr>
<tr>
<td>Aspirin</td>
<td>Aspirin, Caprin®, Nu-Seals®, Gencardia®, Micropirin®</td>
<td>75 mg, 300 mg</td>
<td>Mild to moderate pain, pyrexia, anti-platelet</td>
<td>E/C tablets</td>
</tr>
<tr>
<td>Bisacodyl</td>
<td>Bisacodyl</td>
<td>5 mg</td>
<td>Constipation</td>
<td>E/C tablets</td>
</tr>
<tr>
<td>Budesonide</td>
<td>Budenofalk®, Entocort®</td>
<td>3 mg</td>
<td>Mild to moderate Crohn’s disease</td>
<td>Capsules, enclosing E/C pellets</td>
</tr>
<tr>
<td>Diclofenac sodium</td>
<td>Voltarol®, Arthrotec®</td>
<td>50 mg + 200 mg misoprostol, 75 mg + 200 mg misoprostol 25 mg 25 mg E/C pellets + 50 mg M/R pellets</td>
<td>Pain and inflammation in rheumatic disease and other musculoskeletal disorders; acute gout; postoperative pain</td>
<td>E/C tablets, Capsules</td>
</tr>
<tr>
<td>Didanosine</td>
<td>Videx®</td>
<td>25 mg</td>
<td>HIV infection in combination with other antiretroviral drugs</td>
<td>E/C tablets</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Erythromycin, Erymax®</td>
<td>250 mg</td>
<td>Oral, skin, and respiratory-tract infections, campylobacter enteritis, syphilis, non-gonococcal urethritis, chronic prostatitis</td>
<td>Capsules, enclosing E/C microgranules</td>
</tr>
<tr>
<td>Lansoprazole</td>
<td>Zoton®</td>
<td>15 mg</td>
<td>Gastric and duodenal ulcers</td>
<td>Capsules, enclosing E/C granules</td>
</tr>
<tr>
<td>Chemical name</td>
<td>Brand names</td>
<td>Dose</td>
<td>Indications</td>
<td>Formulation</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>----------------------------------</td>
<td>----------</td>
<td>-----------------------------------------------------------------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>Mecysteine hydrochloride</td>
<td>Visclair®</td>
<td>100 mg</td>
<td>Asthma, Chronic bronchitis, Cystic fibrosis</td>
<td>E/C tablets</td>
</tr>
<tr>
<td>Mesalazine</td>
<td>Asacol® MR, Ipocol®, Mesren® MR, Salofalk®</td>
<td>250 mg, 400 mg</td>
<td>Mild to moderate ulcerative colitis</td>
<td>E/C tablets</td>
</tr>
<tr>
<td>Mycophenolic acid (as mycophenolate sodium)</td>
<td>Myfortic®</td>
<td>180 mg</td>
<td>Prophylaxis of acute renal, cardiac, or hepatic transplant rejection</td>
<td>E/C tablets</td>
</tr>
<tr>
<td>Naproxen</td>
<td>Naproxen, Naprosyn®</td>
<td>250 mg</td>
<td>Pain and inflammation in rheumatic disease and other musculoskeletal disorders; acute gout; postoperative pain</td>
<td>E/C tablets</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>Omeprazole, Losec®</td>
<td>10 mg</td>
<td>Gastric and duodenal ulcers</td>
<td>Capsules, enclosing E/C granules</td>
</tr>
<tr>
<td>Pancreatin</td>
<td>Nutrizym®, Pancrex®, Colpermin®, Creon®, Pancrease HL®, Pancrease®</td>
<td>Providing different minimum units of protease, lipase, and amylase</td>
<td>Pancreatin supplements</td>
<td>Capsules, enclosing E/C beads, pellets, granules, or minitablets</td>
</tr>
<tr>
<td>Pantoprazole</td>
<td>Protium®</td>
<td>20 mg</td>
<td>Gastric and duodenal ulcers</td>
<td>E/C tablets</td>
</tr>
<tr>
<td>Peppermint oil</td>
<td>Colpermin®, Mintec®</td>
<td>0.2 ml</td>
<td>Abdominal colic and distension</td>
<td>E/C soft capsules</td>
</tr>
</tbody>
</table>

Table 1.1. Medicines available as enteric-coated products in the UK (2007). (Continued)
Table 1.1. Medicines available as enteric-coated products in the UK (2007). (Continued)

<table>
<thead>
<tr>
<th>Chemical name</th>
<th>Brand names</th>
<th>Dose</th>
<th>Indications</th>
<th>Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisolone</td>
<td>Prednisolone</td>
<td>2.5 mg, 4 mg</td>
<td>Inflammatory and allergic disorders; inflammatory bowel disease; asthma; immunosuppression; rheumatic disease;</td>
<td>E/C tablets</td>
</tr>
<tr>
<td>Rabeprazole sodium</td>
<td>Pariet®</td>
<td>10 mg</td>
<td>Gastric and duodenal ulcers</td>
<td>E/C tablets</td>
</tr>
<tr>
<td>Rowachol</td>
<td>Rowachol®</td>
<td>Mixture of borneol 5 mg, camphene 5 mg, cineole 2 mg, menthol 32 mg, menthone 6 mg, pinene 17 mg</td>
<td>Biliary disorders</td>
<td>E/C soft capsules</td>
</tr>
<tr>
<td>Rowatinex</td>
<td>Rowatinex®</td>
<td>Mixture of anethol 4 mg, borneol 10 mg, camphene 15 mg, cineole 3 mg, fenchone 4 mg, pinene 31 mg</td>
<td>Urolithiasis</td>
<td>E/C soft capsules</td>
</tr>
<tr>
<td>Sodium valproate</td>
<td>Epilim®</td>
<td>200 mg</td>
<td>All forms of epilepsy</td>
<td>E/C tablets</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>Sulfasalazine, Sulazine®, Salazopyrin®</td>
<td>500 mg</td>
<td>Mild to moderate and severe ulcerative colitis; active Crohn's disease; rheumatoid arthritis</td>
<td>E/C tablets</td>
</tr>
<tr>
<td>Typhoid vaccine</td>
<td>Vivotif®</td>
<td>Attenuated Salmonella typhi (Ty21a)</td>
<td>Typhoid immunisation</td>
<td>E/C capsules</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>Convulex®</td>
<td>150 mg</td>
<td>Manic episodes associated with bipolar disorder</td>
<td>E/C capsules</td>
</tr>
</tbody>
</table>

E/C: enteric coated; M/R: modified release
1.2.1 Overview of the GI tract

The GI tract is a hollow muscular tube extending from the mouth to the anus (Figure 1.1). Following the mouth is the esophagus. The length of the GI tract from the esophagus to the anus is approximately 9 m. The major functions of the GI tract are ingesting food, digesting it to extract energy and nutrients and expelling the remaining waste. The GI tract is divided into three key regions: the stomach, small intestine and large intestine. Each region has certain anatomical and physiological features, which are necessary for accomplishing specific functions.

Figure 1.1. Diagram of the human gastrointestinal tract (courtesy of Genesis Health System, http://www.genesishealth.com).
The stomach monitors the food delivery to the small intestine by acting as a reservoir and processing food into fluid chyme. In addition, protein from food is mainly digested in the stomach by pepsins. The stomach has three main regions: fundus, body and antrum.

The small intestine is enriched of digestive enzymes and facilitated large surface area by the presence of microvillii in the mucosa. This makes it as the main site for food digestion and absorption in the GI tract. The small intestine can also be divided into three sections: duodenum (the first 0.2-0.3 m); jejunum (the second 2.5 m) and ileum (the final 3.5m).

The large intestine is approximately 1.2-1.5 m in length and comprises the caecum, colon, rectum and anus. It is responsible for the formation and storage of faeces by removing a large amount of water content from the indigestible material and finally functions defecation. The main functions of the large intestine are preformed by the colon, which is further subdivided into the ascending (20 cm), transverse (45 cm), descending (30 cm) and sigmoid colon (40 cm).

1.2.2 pH in the GI tract

A typical pH-profile of the normal GI tract was reported by Evans et al. (1988) (Figure 1.2). The stomach presents an acidic pH condition, mostly below 3. From the stomach to the duodenum, a sharp rise in pH occurs. The pH level gradually increases down the small bowel. The mean pH values reported by Evans et al. (1988) were: 6.63 in the jejunum, 7.41 in the mid small intestine and 7.49 in the ileum. A sharp drop in the luminal pH occurs from the terminal ileum to the caecum by about 1.5 pH units, and the pH level then gradually rises again along the colon.
Despite widespread quotation of this pH profile, it only represents the pH profile of one normal subject. It has subsequently been shown that inter/intra-subject luminal pH vary significantly (Ibekwe, 2006). In addition, several factors influence the pH-profile of the GI tract, such as age, gender, gastrointestinal diseases and most importantly, the presence and composition of food (Gardham and Hobsley, 1970; Youngberg et al., 1987; Russell et al., 1993; Press et al., 1998; Shih et al., 2003). These factors, as well as the details of the different regional pH of the GI tract are discussed in the following sections.

1.2.2.1 Gastric pH

The gastric pH can be very different with or without the presence of food. The fasted gastric pH has been well studied, with little variation among the results obtained. The generally accepted value for fasted gastric pH is approximately pH 2, ranging.
from 1.0-3.5, predominantly 1.0-2.5 (Ovesen et al., 1986; Youngberg et al., 1987; Evans et al., 1988; Fallingborg et al., 1989; Dressman et al., 1990; Fallingborg, 1999).

Eating of a meal stimulates gastric acid secretion; however, this increase in acid level is normally exceeded by the buffering effect of the food, resulting in the rise of the intragastric pH (Malagelada et al., 1976; Ladas et al., 1983; Dressman et al., 1990). The level of this intragastric pH increase varies depending on the meal composition; the range is from 4.0 to 5.0 and the peak value can be raised to above 6.0. Meals which have higher buffering effects such as meals high in protein contents can buffer the gastric pH to a higher peak pH compared to meals high in carbohydrate or fat contents.

The gastric pH gradually declines to the fasted value after the meal is completed due to the increasing acid output, which overwhelms the buffering capacity of the food. The volume and composition of the meal also determines the decline rate of gastric pH by both the ability of the meal to stimulate gastric acid secretion and the rate at which the meal is emptied from the stomach. The larger the meal size, the longer the emptying time, thus contributes to the longer time needed to return to the fasted value. In most reported studies, the time for restoration of the fasted state pH is within 2 hours. Table 1.2 gives the gastric pH after different meals.

The increase in intragastric pH after a meal has implications on the gastric-resistance of enteric-coated dosage forms. Enteric coatings based on pH-dependent polymers are designed to be insoluble in the acidic conditions of the stomach. However, enteric-coated products which show good acid-resistance in the low pH conditions of the fasted stomach, may perform differently in raised gastric pH values of 3-4 or higher, if administrated with or shortly after a meal. This may cause premature drug release in the stomach or the degradation of the protected acid-labile drugs.
Table 1.2. *Gastric pH after different meals*

<table>
<thead>
<tr>
<th>Composition of the meal*</th>
<th>Fasted pH</th>
<th>Peak pH after meal</th>
<th>Time to return to pH &lt; 3.0 after completion of meal (minutes)</th>
<th>Time to return to pH &lt; 2.0 after completion of meal (minutes)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>2.0</td>
<td>5.0</td>
<td>60</td>
<td>120</td>
<td>(Malagelada et al., 1976)</td>
</tr>
<tr>
<td>B</td>
<td>1.7 (1.4-2.1)</td>
<td>6.7 (6.4-7.0)</td>
<td>45 (2-158)</td>
<td>96 (8-240)</td>
<td>(Dressman et al., 1990)</td>
</tr>
<tr>
<td>C</td>
<td>2.4 ± 0.8</td>
<td>3.9 ± 1.7</td>
<td>-</td>
<td>45 (return to the fasted level)</td>
<td>(Ladas et al., 1983)</td>
</tr>
</tbody>
</table>

* A: 90 g (uncooked weight) of tenderloin steak; 25 g of white bread with 8 g of butter; 60 g of vanilla ice cream topped with 35 g of chocolate syrup; 240 ml water. The meal contained approximately 40% carbohydrate, 40% fat and 20% protein. The total caloric value of the meal was 458 kcal.

B: 6 oz (170 g) of hamburger; 2 slices of bread; 2 oz (56.7 g) of hash brown potatoes, 1 tablespoon ketchup and mayonnaise; 1 oz (28.35 g) each of tomato and lettuce and 8 oz (226.8 g) of milk. The total caloric value of the meal was 1000 kcal.

C: two doughnuts (62 g each) and 250 ml of pasteurized cows' milk containing 30 g of sucrose. The meal contained approximately 10% of protein, 20% of fat, and 70% of carbohydrate. The total caloric value of the meal was 750 kcal.

### 1.2.2.2 pH in the small intestine and colon

The acidic content arriving from the stomach is neutralized by bicarbonate secreted into the duodenum by the pancreas. This is responsible for a drastic increase in the pH values from the stomach to the duodenum. The lumen pH of the proximal small intestine usually lies within the range of 5.5 to 7.0, gradually increasing by about 1 pH unit to 6.5-7.5 in the distal ileum. The alkalization of the luminal fluid along the gut is most likely due to the secretion of bicarbonate into the lumen by the intestinal epithelium, combined with the absorption of bile acid, which is secreted by the liver to the lumen, from the intestinal fluid (Borgstrom, 1974). There is a sharp fall in luminal pH from the terminal ileum to the caecum (5.5-7.0), due to bacterial
fermentation of nonabsorbed carbohydrates to short chain fatty acids. The pH value of the right colon is approximately the same as in the caecum and then rises in the left colon and rectum to 6.0-7.5 (Evans et al., 1988; Fallingborg et al., 1989; Pye et al., 1990).

The pH values of the proximal small intestine determine the time and site of the disintegration of enteric-coated dosage forms based on pH-dependent coatings. To evaluate the *in vivo* performance of enteric-coated products, a through understanding of the pH conditions in this part of the gut is needed.

At the first part of the duodenum is the duodenal bulb. This is the portion of the duodenum which is closest to the stomach and adjacent to the pyloric sphincter (Figure 1.3). Bicarbonate secreted into the duodenum is retropulsed to the duodenal bulb and increases its pH level. However, the duodenal bulb pH shows rapid and wide fluctuations due to the influence of several factors: acidity of gastric contents, rate of gastric emptying, bicarbonate secretion into the duodenum and its retropulsion to the bulb (Hannibal and Rune, 1983). This area also has a steep pH gradient, which makes it difficult to determine a mean pH value. A method was reported to measure the duodenum bulb pH with small glass electrodes tied together at 1.5 cm intervals from the stomach to the proximal duodenum (Rune, 1968; Hannibal and Rune, 1983; Bendtsen et al., 1987). The results showed an acidic duodenum bulb pH around 2-3 (Hannibal and Rune, 1983; Ovesen et al., 1986; Bendtsen et al., 1987).

Following the rapid pH increase in the proximal duodenum, the mid to distal duodenum shows more stable pH values. Table 1.3 summarises the pH values of the proximal small intestine including duodenum and jejunum in the literature in healthy humans. As reported in these studies, the proximal jejunum pH is slightly lower than that of the duodenum. This is attributed to the acidifying process caused by the absorption of bicarbonate in the proximal jejunum (Wright et al., 1979).
Figure 1.3. Location of the duodenal bulb. Adapted from the Wikipedia, http://en.wikipedia.org/wiki/Duodenal_bulb.

Table 1.3. Luminal pH values of the duodenum and jejunum in healthy humans (mean (±SD))

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of subjects</th>
<th>Method of measurement</th>
<th>Duodenum pH</th>
<th>Jejunum pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Rune and Viskum, 1969)</td>
<td>8</td>
<td>Glass electrode</td>
<td>6.3 (±0.9)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td></td>
<td>1st Part: 6.0 (±0.5)</td>
<td>5.8 (±1.0) (7 subjects)</td>
</tr>
<tr>
<td>(Benn and Cooke, 1971)</td>
<td>11</td>
<td>Glass electrode</td>
<td>2nd Part: 6.7 (±0.4)</td>
<td>3rd Part: 6.4 (±0.6)</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td></td>
<td>1st Part: 4.7 (±1.5)</td>
<td>5.3 (±1.3) (7 subjects)</td>
</tr>
<tr>
<td>(Benn and Cooke, 1971)</td>
<td>11</td>
<td>Aspiration</td>
<td>2nd Part: 5.4 (±1.5)</td>
<td>3rd Part: 6.1 (±1.5)</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td></td>
<td>Midduodenum: 4.90 (4.00-5.39)</td>
<td>Proximal: 4.92 (4.65-5.70)</td>
</tr>
<tr>
<td>(Ovesen et al., 1986)</td>
<td>14</td>
<td>Glass electrode</td>
<td>4.90 (4.00-5.39)</td>
<td>5.95 (5.11-5.98)</td>
</tr>
<tr>
<td>(Fallingborg et al., 1989)</td>
<td>39</td>
<td>RCS</td>
<td>6.4 (median)</td>
<td>-</td>
</tr>
<tr>
<td>(Dressman et al., 1990)</td>
<td>34</td>
<td>HC</td>
<td>6.1 (5.8-6.5)</td>
<td>-</td>
</tr>
<tr>
<td>(Fallingborg et al., 1994)</td>
<td>10</td>
<td>RCS</td>
<td>6.25 (±0.08)</td>
<td>Proximal: 6.06 (±0.08)</td>
</tr>
</tbody>
</table>

RCS: Remote Control System capsule; HC: Heidelberg capsule
The reported mean duodenum pH values varied in these studies. This is probably due to the different pH measurements used. The methods for investigating the intestinal lumen pH include: aspiration method, pH electrode intubations and tubeless radiotelemetry capsules. The aspiration technique was employed by the earlier researchers and the aspirated fluids from the different segments of the GI tract were measured in vitro using standard glass electrode. One difficulty in using this technique is being able to obtain an adequate amount of fluid in a certain region of the small intestine within a short time. The measured small intestine pH can be lower than the actual value due to the possible contamination of the aspirates by the acidic gastric fluid when passing the stomach.

The pH electrode intubation normally involves fixing a series of glass electrodes in a tube at specific intervals. The tube is then passed through the mouth or nasal passage down to the intestine and the electrodes place at different parts of the intestine. The advantage of this approach is that the location of the electrodes can be manipulated to the desired position and the obtained pH value can clearly indicate that of different segments of the intestine. The disadvantage is that the procedure is uncomfortable for the subject.

Tubeless radiotelemetry capsules are now more often employed to investigate the pH of the gut, due to the provision of a non-invasive approach. The capsules normally comprise a pH electrode and a radio transmitter with a size suitable for oral ingestion. The most commonly used capsules of such kind are Heidelberg capsule and Remote Control System capsule. The capsules can be used tethered and un-tethered. The tethered method involves in attaching the capsule with a tether, which can still cause inconvenience to the subject. The un-tethered method is also called “free fall” method, where the capsule passes down the GI tract freely.
Despite the approach being more elegant and convenient to apply, the radiotelemetry technique has limitations with respect to the accuracy of the obtained pH value. The desired accuracy for the Heidelberg capsule was 0.5 pH unit (Youngberg et al., 1987) and Fallingborg et al. (1990a) measured the accuracy of Remote Control System capsule as 0.3 pH unit. A frequency drift is also commonly observed for both of the above capsules, with the maximum drift of 0.5 pH unit (Fallingborg et al., 1989; Dressman et al., 1990; Fallingborg et al., 1994). At the end of the study, the capsule is recovered from faeces of the subject and then used for measuring the pH of standard solutions. The pH value obtained is compared to the calibrated glass electrode, and the difference is called the frequency drift. This is caused by the oxidation of the antimony electrode in intestinal fluid.

In the case of measuring the pH value of the proximal small intestine, another problem for the un-tethered radiotelemetry capsules is the rapid transit of the capsules through this region, resulting in less accurate pH measurement. For this reason, the proximal small intestine pH obtained from glass electrodes and tethered capsules is seen as more reliable. In the measurements listed in Table 1.3, the un-tethered capsule measurement of the proximal small bowel was applied by Fallingborg et al. (1989).

The consumption of a meal also has an influence on the small intestine luminal pH, especially the proximal part of the small bowel. The arrival of the acidic chyme from the stomach at first decreases the luminal pH but later the fasted pH value is re-established as a result of pancreatic bicarbonate output. The duodenal pH is directly influenced by food. Dressman et al. (1990) measured the median fasted duodenal pH as 6.1 using Heidelberg capsules. During the meal, a brief period of elevated duodenal pH was observed, with the median pH value as 6.3. This can be attributed to the cephalic phase of pancreatic bicarbonate secretion. However, the duration of this pH increase is very short, 5-10 minutes as reported by Youngberg et al. (1987). In the same study, Dressman et al. (1990) showed that the overall pH in
the fed phase of the duodenum is considerably lower than in the fasting state, around 5.4 (3.1-6.7). Following the duodenum, the proximal jejunal pH also decreases after a meal, to the range of 5.2 to 6.0 (Ovesen et al., 1986).

However, in a latest study, Bratten and Jones (2006) placed the radiotelemetry capsules in the duodenum of 25 healthy subjects using endoclips for 48 hours. The duodenum pH values were recorded at 15 minutes intervals. The mean pH value did not differ between meal (5.67, range 5.42-5.93), sleep (5.56, range 4.87-6.24) and fasting (5.44, range 5.07-5.80) periods. In all of these three stages, there were time periods with duodenal pH < 2.5, and in fasting and sleep stage these time periods were proportionately greater than fed stage.

Several studies demonstrated no significant difference in GI pH due to gender (Dressman et al., 1990; Russell et al., 1993; Shih et al., 2003). Shih et al. (2003) also reported that gastric acid secretion does not change with age. Fallingborg et al. (1990b) found that the pH profiles in 8-14 years old children are almost identical to that of healthy adults. Russell et al. (1993) investigated the upper GI pH of elderly North Americans and showed that the majority of elderly subjects exhibited fasted gastric pH profiles similar to those of the young subjects. However, nine of 79 subjects had a median fasted gastric pH greater than 5. Following a meal, the rate of return to fasted pH was considerably slower in elderly than young subjects.

Patients with various diseases may have significantly different GI pH profiles compared to the healthy people. The gastric pH of patients with pernicious anaemia can be as high as pH 7-8 (Gardham and Hobsley, 1970). Patients with Crohn’s disease have significantly higher median gastric pH compared to healthy subjects. The pH values in the terminal ileum, caecum and the right colon are also higher in these patients compared to healthy people, although the pH values in the proximal small intestine and in the left colon are similar as the healthy people (Press et al., 1998; Nugent et al., 2001). It was observed that the duodenal pH in the fed stage
was consistently lower in Cystic Fibrosis patients than in healthy subjects (Youngberg et al., 1987; Robinson et al., 1990).

1.2.3 GI transit

The GI transit of pharmaceutical dosage forms is commonly investigated using the technique of \( \gamma \)-scintigraphy. Dosage forms are radiolabelled with radionuclides, most popularly \( {^{99m}} \text{Tc} \). The transit of the labelled dosage forms along the GI tract is then recorded by acquiring sequential static images using a gamma camera. By applying anatomical reference marker, gastric emptying, small intestinal and colonic transit of dosage forms can be identified.

From the pharmaceutical point of view, \( \gamma \)-scintigraphy also offers an approach to evaluate the \textit{in vivo} performance of oral drug delivery systems. The time and position of the disintegration of dosage forms can be visualized and quantified. \( \gamma \)-scintigraphy allows simultaneous determination of the GI transit and the disintegration, which is particularly of value for assessing the \textit{in vivo} performance of enteric-coated dosage forms by providing the lag time of disintegration post gastric emptying.

1.2.3.1 Gastric emptying

\textit{Gastric emptying of meal}

The gastric emptying patterns and rates of different components of a meal vary for liquid, digestible solid and indigestible solid in the meal. The separation of the liquid from the solid of a meal is rapid, and the liquid empties more rapidly than the solid. The digestible solid then empties following the liquid (Notivol et al., 1984), and the large indigestible solid empties only after all the food had left the stomach. The \( T_{1/2} \) (the time for half the component to be emptied) values of these three parts of meal
have been reported in a study to be 30 ± 3 minutes, 154 ± 11 minutes and 3 to 4 hours for liquid, digestible solid and indigestible solid respectively (Feldman et al., 1984).

Gastric emptying of liquids is controlled mainly by the gradient in pressure between the stomach and duodenum. The proximal stomach produces slow sustained contractions regulating the intragastric pressure. Therefore, the rate of liquid emptying is primarily determined by the contractions of the proximal stomach (Kelly, 1980; Minami and McCallum, 1984). The volume and calorie content of the meal are also factors influencing the gastric emptying rate of liquid meal. High-calorie and large meals take longer time to leave the stomach than low-calorie and small meals (Brunner et al., 1974).

The emptying of solid is the function of the contractions of the distal stomach comprising the antrum and pylorus. The solid food is propelled toward the pylorus and duodenum by the peristaltic waves of the distal stomach but is not able to pass through the narrow pylorus unless its size is less than 1-2 mm (Meyer et al., 1979). The large pieces of solid meal are grinded and triturated by the peristaltic wave of the distal stomach and retropulsed back toward the more proximal stomach. This process repeats to break down the solid size until they are small enough to pass through the pylorus (Carlson et al., 1966).

The mechanism of eliminating indigestible solids from the stomach is different from that of liquid and digestible solids and is related to a distinct cycle of electromechanical activity of the stomach during fasting state. This cycle is described as the migrating motor complex (MMC), starting in the proximal stomach and migrating aborally through the small intestine (Code and Marlett, 1975). The complex recurs approximately every 2 hours and composes of four phases. Phase I lasts about 60 minutes and has few or no action potentials and contractions. Phase II appears over a 30-45 minutes period and has intermittent peristaltic contractions. In
phase III, there are intense bursts of contractions generated by action potentials occurring with every pacesetter potential over a 5-10 minutes period. A short phase IV follows phase III, with the contractions slacking up and then phase I begins again. The emptying of indigestible solids takes place during late phase II and early phase III of the MMC cycles. The strong activity of phase III acts as “housekeeper” of the GI tract and sweeps any remaining solid out of the stomach (Kelly, 1980; Minami and McCallum, 1984; Feldman et al., 1984).

**Gastric emptying of dosage forms**

Modified release dosage forms which do not disintegrate in the stomach will be emptied from the stomach into the small intestine. Large non-disintegrating (single-unit) dosage forms such as tablets are emptied from the stomach in the same manner as indigestible solid in the meal and highly dependent on the condition of the stomach. In the fasted state, large non-disintegrating dosage forms are swept out from the stomach by the “housekeeper” wave during the phase III of the MMC (Davis et al., 1988). If the dosage forms are administered with or shortly after a meal, the interdigestive MMC cycle is interrupted by the fed state of the stomach. In these cases, the emptying of the dosage forms only take place during the next phase III of the MMC, when all of the food has left the stomach and the fasted state is resumed. Therefore, the gastric emptying of these dosage forms is fairly fast when administered in the fasted stomach, normally in less than 2 hours and in most cases within 1 hour (Park et al., 1984; Davis et al., 1986c; Marvola et al., 1987; Khosla and Davis, 1989; Ofori-Kwakye et al., 2004). There will be inter- and intra-subject variability depending on the arrival time of the dosage forms in the stomach in relation to the contractile activity of the MMC.

However, the phase III contraction is not always efficient to sweep the dosage forms out of the stomach. In some cases, the large non-disintegrating dosage forms did not empty from the fasted stomach; and the following feeding (4 hours
post-administration) further delayed the emptying (Khosla and Davis, 1989; Ibekwe et al., 2006b). Coupe et al. (1991a) reported that the Remote Control System capsule remained in the stomach for more than 12 hours, even though phase III contractions were noted at 4.5, 6.5 and 8.5 hours postdose. This prolonged retention in the fasted stomach could be explained by the fact that the dosage forms are located in the less muscular body of the stomach and was not propelled into the antrum where emptying could take place.

The presence of food in the stomach can significantly prolong the gastric retaining time for large single-unit dosage forms due to the interruption of the MMC cycle. Therefore, the gastric emptying times for these dosage forms in the fed state highly depend on the volume and composition of the food and become very unpredictable. The variability of gastric emptying time for large single-unit dosage forms has clear implications on the bioavailability of the containing actives. Therefore, there is a general agreement that multi-units such as pellets are superior to large single-unit dosage forms, in terms of that gastric emptying is less influenced by the condition of the stomach and the presence of food, and thus, is less variable.

Although studies have proved that gastric emptying of small granules or pellets is indeed faster and less variable than large single unites in fed state (Davis et al., 1986b; Kaniwa et al., 1988a; Kaniwa et al., 1988b; Feely and Davis, 1989; Abrahamsson et al., 1996), the situation is more complicated than one would assume. Firstly, the gastric emptying of pellets is unlike the behaviour of liquids nor concurrent with the coadministered meal; a prolonged gastric resident time is commonly observed in fed state (Kaniwa et al., 1988a; Kaniwa et al., 1988b; Feely and Davis, 1989; Coupe et al., 1993; Clark et al., 1993; Abrahamsson et al., 1996). Apart from the influence of food, some formulation factors such as the density of the pellets can also affect the gastric emptying rate (Devereux et al., 1990; Clark et al., 1993).
Secondly, the cutoff size below which pellets can empty in the fed stage remains controversial. It is often quoted as 1-2 mm, as adapted from animal results (Kelly, 1981). However, Coupe et al. (1991a) reported that tablets with 7 mm diameter can empty from the fed stomach with food. Other research groups have also observed similar results (Davis et al., 1988; Khosla et al., 1989; Timmermans and Moes, 1993). Khosla and Davis (1990) even found that fed state emptying can take place with tablets up to 11 mm in diameter. The conclusion described by Khosla and co-workers (1989) is therefore feasible, that “there is no exact cutoff size of gastric emptying, but a gradation of size over which predictable emptying from a fed stomach becomes uncertain and highly variable”.

1.2.3.2 Small intestinal transit time

The aboral movement of the intestinal contents is also associated with the MMC, especially the powerful bursts of contractions of phase III, which sweeps slowly from the stomach to the ileum (Szurszewski, 1969). The MMC occurs throughout the human small intestine, but the velocity of migration decreases with distal progression along the small intestine. As measured by Kerlin and Phillips (1982), the velocity of aboral migration of the MMC was 4.7 ± 1.8, 1.3 ± 0.4, and 0.9 ± 0.2 cm·min⁻¹ in the jejunum, ileum, and terminal ileum, respectively. The transit of dosage forms through the duodenum is very fast due to the short distance of this region of the small intestine and fast initial transit rate. After passing through the duodenum, the dosage form moves through the small intestine at between 4.2 and 5.6 cm per minute (Kaus et al., 1984). This velocity is close to the rate of migration of the MMC along the intestine.

Davis et al. (1986b) reported the average small intestinal transit time of 3-4 hours for dosage forms. The authors also found that there is no statistical difference in intestinal transit behaviour for solutions, pellets and single units for both the fasted
and fed states. This consistency of small intestinal transit as well as the range of the
transit time has been agreed by many other researchers (Kaus et al., 1984; Mundy et
al., 1989; Khosla and Davis, 1989; Adkin et al., 1993; Abrahamsson et al., 1996;
Billa et al., 2000).

However, a few research groups have reported the differential small intestinal transit
of dosage forms. Clark et al. (1993) showed that small intestinal residence time was
significantly prolonged by both the increase in pellet density and size. The influence
of pellet density on transit time was in agreement with the findings of Bechgaard
and Ladefoged (1978). Feeding was showed having influence on small intestinal
transit times of multiparticulates by Digenis et al. (1990). Enteric-coated pellets
were administered in a hard gelatine capsule under fasted and non-fasted conditions.
The non-fasted study in this test was unusual to other experiments since the dosage
form was actually administered under the fasted condition and was subsequently
followed by a standard breakfast meal at 30 minutes post-capsule administration.
They found that the small intestine transit was more rapid in the non-fasted
condition compared to the fasted condition. This result indicates that eating has
accelerated the small intestine transit of the pellets.

Excepients used in dosage forms can also influence the small intestine transit.
Polyethylene glycol 400 was found to decrease the small intestine transit time in
male volunteers and leading to the reduction in the bioavailability of
coadministered ranitidine (Basit et al., 2001; Schulze et al., 2003). This effect was
dose dependent even at low concentrations of polyethylene glycol 400.

In addition, although the average small intestine transit time was reported to be
consistent, inter and intra-subject variability is significant. In the study by Davis et
al. (1986b) the transit time for single unit dosage forms is actually in the range of
0.5-7 hours. For pellets, in one subject the transit time is longer than 9 hours. Coupe
et al. (1991b) reported a significant intra-subject variability of small intestine transit
times. In 4 study periods, the largest intra-subject variations are 162 minutes (range 190-352 minutes) and 206 minutes (range 165-371 minutes) for single-unit and multi-unit dosage forms respectively.

After passing through the small intestine, the multi-unit dosage forms which spread through the small intestine due to the different gastric emptying times were observed to regroup at the ileo-caecal junction (ICJ) (Bechgaard and Ladefoged, 1978; Khosla et al., 1989; Khosla and Davis, 1989; Adkin et al., 1993). The large single-unit dosage forms are held in the ICJ for extended periods before they are transferred into the caecum (Khosla and Davis, 1989; Adkin et al., 1993; Ibekwe et al., 2006b). The stagnation times at the ICJ are in the range of 2-10 hours (Davis, 1989). Feeding has been observed to be associated with short ICJ stasis time; the phenomena was known as “the gastrocolonic response” (Spiller et al., 1987; Adkin et al., 1993; Ibekwe et al., 2006b). The motility of the terminal ileum increases upon the ingestion of food, and tends to clear of the residue from the previous meals.

1.2.4 Electrolytes secretion in GI tract

The electrolyte composition in the GI tract also influences the performance of enteric coatings. The dissociation rate of pH-responsive enteric polymers depends on the electrolyte environment; thus influencing the dissolution of the enteric coating and correspondent drug release (Hayashi et al., 1970; Kararli et al., 1995; Chan et al., 2001; Fadda and Basit, 2005).

1.2.4.1 Electrolytes in gastric secretion

The main electrolytes in gastric secretion are H⁺, Cl⁻, K⁺, Na⁺ and Ca²⁺. Table 1.4 gives the mean concentration of electrolytes in gastric juice.

24
Table 1.4. Concentration of electrolytes in gastric juice (mmol/l)

<table>
<thead>
<tr>
<th></th>
<th>(Lindahl et al., 1997) (n = 36, means±SD)</th>
<th>(Basil, 1961) (means±SEM)</th>
<th>(Semb, 1966) (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H⁺</td>
<td>-</td>
<td>27.5±2.1 (n=31)</td>
<td>40.0 (10-90)</td>
</tr>
<tr>
<td>Cl⁻</td>
<td>102±28</td>
<td>99.9±2.2 (n=23)</td>
<td>114 (84-141)</td>
</tr>
<tr>
<td>K⁺</td>
<td>13.4±3.0</td>
<td>15.2±0.27 (n=22)</td>
<td>14.1 (9-17)</td>
</tr>
<tr>
<td>Na⁺</td>
<td>68±29</td>
<td>58.2±3.1 (n=10)</td>
<td>62.6 (30-121)</td>
</tr>
<tr>
<td>Ca²⁺</td>
<td>0.6±0.2</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Patients with GI disease can have different values of gastric electrolytes secretion. Table 1.5 provides the concentration of main electrolytes in gastric juice in patients with GI disease (Basil, 1961).

Table 1.5. Concentration of electrolytes in gastric juice in patients with GI disease (mmol/l, means±SEM)

<table>
<thead>
<tr>
<th></th>
<th>Duodenal ulcer</th>
<th>Gastric ulcer</th>
<th>Gastric cancer</th>
<th>Gastritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>H⁺</td>
<td>43.3±2.6</td>
<td>15.3±1.7</td>
<td>1.9±0.1</td>
<td>1.2±0.5</td>
</tr>
<tr>
<td>Cl⁻</td>
<td>117.9±1.8</td>
<td>111.1±1.7</td>
<td>86±3.0</td>
<td>81.3±2.8</td>
</tr>
<tr>
<td>K⁺</td>
<td>14.3±0.49</td>
<td>15±0.47</td>
<td>17.7±0.56</td>
<td>16.6±0.72</td>
</tr>
<tr>
<td>Na⁺</td>
<td>51.5±2.9</td>
<td>76.3±2.8</td>
<td>67.1±3.5</td>
<td>67.1±3.5</td>
</tr>
</tbody>
</table>

Alkaline gastric juice can also be found in patients with pernicious anaemia, and can occasionally be found, under resting circumstances, from many other subjects. The alkaline gastric juice has a pH as 7-8, and a decreasing concentration of sodium and chloride, with increasing potassium (Gardham and Hobsley, 1970).
1.2.4.2 Electrolytes in intestinal secretion

The principle characteristic of intestinal secretion is the secretion of bicarbonate by the pancreas into the proximal part of the duodenum. This ensures the quick change of acidic gastric juice to a higher near neutral pH. In addition, other electrolytes such as Cl⁻, K⁺, Na⁺, Mg²⁺, and Ca²⁺ also exist in the luminal fluids and play a role in orchestrating water and nutrient absorption. Table 1.6 gives the mean concentration of electrolytes in the intestinal juice.

**Table 1.6. Concentration of electrolytes in intestinal juice (mmol/l, means±SD)**

<table>
<thead>
<tr>
<th></th>
<th>Jejunum</th>
<th>Jejunum</th>
<th>Ileum</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCO₃⁻</td>
<td>-</td>
<td>8.2±5</td>
<td>30±11</td>
</tr>
<tr>
<td>Cl⁻</td>
<td>126±19</td>
<td>135±8</td>
<td>125±12</td>
</tr>
<tr>
<td>K⁺</td>
<td>5.4±2.1</td>
<td>4.8±0.5</td>
<td>4.9±1.5</td>
</tr>
<tr>
<td>Na⁺</td>
<td>142±13</td>
<td>142±7</td>
<td>140±6</td>
</tr>
<tr>
<td>Ca²⁺</td>
<td>0.5±0.3</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

1.3 MATERIALS USED FOR ENTERIC COATINGS

1.3.1 Historical development of enteric coating materials

The earliest documentation of enteric-coated oral solid dosage forms can be traced back to the late nineteenth century. The first real enteric coating was believed to use
keratin by Unna in 1884. Other materials used for enteric coatings at earlier times included salol, formalized gelatin and stearic acid (Agyilirah and Banker, 1991). Among these materials, stearic acid which relies on the break down by pancreatic enzymes and solubilization by bile salts in the small intestine, was believed to be the most effective (Freeman, 1928; Worton et al., 1938). Although no longer of commercial interest, the development of enteric coatings which disintegrate in the small intestine due to the sensitivity to pancreatic lipase still remains of interest in pharmaceutical research (Yoshitomi et al., 1992).

Since the 1930s, the natural polymer, shellac, secreted by the lac insect (*Karria lacca*) has been used for enteric coatings based on its pH-dependent solubility (Wruble, 1930). For a long time, it remained the main enteric polymer of choice for the food and pharmaceutical industries. Although the natural origin of shellac grants it non-toxicity, it also generated problems such as batch-to-batch variation and occasional supply problems (Wang et al., 1999); increased disintegration and dissolution time at storage causing stability problems of coated products; and more importantly, as an enteric polymer, dissolving at relatively high pH values (pH > 7.0), due to its high pKₐ of between 6.9 and 7.5 (Cole, 1995).

The above-mentioned materials were not reliable for use as enteric coatings. They were either not able to effectively protect the contents in the stomach or failed to release adequate amounts of active substances in the small intestine (Levy and Jusko, 1967; Madan and Minisci, 1976; Fernando and Moorhead, 1979). In one report by Wagner et al., (1973) enteric-coated commercial sodium aminosalicylate tablet was recovered in faeces and 98% of administered drug was still in the tablet. The coating material used in this case was a fat/wax mixture. It is believed that the decline in the use of enteric-coated products in the early 1980s was due to the unreliability of the performance of enteric-coated dosage forms (Chambliss, 1983).
The suspicion and criticism toward the early enteric-coated products lead to the elimination of many unacceptable enteric coatings and the development of new synthetic or modified natural enteric polymers. Thus, almost all the currently used enteric materials are synthetic or semi-synthetic polymers containing ionizable carboxylic groups. The carboxylic groups of the polymer remain un-ionized in the low pH environment of the stomach, and become ionized in the higher pH conditions of the small intestine. This pH-dependent ionization of their functional groups renders the polymer coatings sufficiently insoluble in the stomach while being able to disintegrate or dissolve in the small intestine, thus releasing their active contents. These enteric polymers can be subdivided into cellulose-based polymers, polyvinyl derivatives and polymethacrylates.

1.3.2 Cellulose-based polymers and polyvinyl derivatives

1.3.2.1 Cellulose-based enteric polymers

Cellulose-based enteric polymers have the same cellulose backbone but the hydroxyl groups of the glucose unit of the cellulose chain are substituted by different substituent groups (as shown in Figure 1.4). These cellulose derivatives can be either obtained from cellulose or from hypromellose (hydroxypropyl methylcellulose, HPMC). The first type includes cellulose acetate phthalate (CAP) and cellulose acetate trimellitate (CAT), and the latter includes hypromellose phthalate (HPMCP) and hypromellose acetate succinate (HPMCAS).

![Figure 1.4. The structure of a substituted cellulose. (R can be represented as \(-H\) or, different substituent groups depending on the individual polymer). Adapted from Hogan (1995).]
CAP is prepared by reacting a partial acetate ester of cellulose with phthalic anhydride. CAT is a chemical resemblance to cellulose acetate phthalate but possesses an additional carboxylic acid group on the aromatic ring. HPMCP is manufactured by treating hypromellose with phthalic acid. HPMCAS is a mixture of acetic acid and monosuccinic acid esters of hypromellose. Table 1.7 shows the substituent groups and solubility of these cellulose-based enteric polymers.

**Table 1.7. Chemical structures and soluble pH values of some cellulose-based enteric polymers**

<table>
<thead>
<tr>
<th>Polymer</th>
<th>Substituent groups</th>
<th>Available type</th>
<th>Soluble at pH above</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAP</td>
<td>-CO-CH₃</td>
<td></td>
<td>6.0</td>
</tr>
<tr>
<td>HPMCP</td>
<td>-CH₃</td>
<td>HP-50</td>
<td>5.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HP-55</td>
<td>5.5</td>
</tr>
<tr>
<td>HPMCAS</td>
<td>-CH₂-CH(OH)-CH₃</td>
<td>MF</td>
<td>5.5</td>
</tr>
<tr>
<td></td>
<td>-CH₂-CH-CH₃</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
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</tbody>
</table>

29
1.3.2.2 Polyvinyl derivatives

The only polyvinyl derivatives used for enteric coatings is polyvinyl acetate phthalate (PVAP). It is produced by the esterification of partially hydrolysed polyvinyl acetate with phthalic anhydride. Figure 1.5 shows the chemical structure of PVAP.

![Chemical structure of PVAP](image)

**Figure 1.5.** Chemical structure of PVAP. Depending on the phthalyl content, \(a\) will vary with \(b\) in mole percent. The acetyl content \(c\) remains constant depending on the starting material. Adapted from Kibbe (2000).

Like other phthalate-containing polymers, the aqueous solubility of PVAP is pH dependent. It is not soluble in low pH media but dissolves at pH values above 5.

1.3.2.3 Factors influencing the solubility of cellulose-based enteric polymers and polyvinyl derivatives

The aqueous solubility of enteric polymers, especially the dissolution rate at a given pH and the threshold pH above which the polymer are soluble, determines the disintegration and dissolution properties of enteric coated products. Factors affecting
the solubility and dissolution of enteric polymers include the structure of the polymer backbone and the type and degree of substituents.

In a study conducted by Davis et al. (1986a), the dissolution rate of three types of phthalate-containing enteric polymer – PVAP, CAP and HPMCP was compared. The authors speculated that the difference in the dissolution rates between these polymers was associated with the different backbone structure of the polymers. PVAP and HPMCP have water-soluble backbones, whereas CAP has water-insoluble backbone. The presence of phthalate groups in the polymer structure was responsible for the gastric-resistance of the polymers; however, the functions of phthalate on influencing the dissolution of the polymers are different. In the case of polymers with a water-soluble backbone, the substitution of phthalate groups which is fairly hydrophobic and unionizable in acid conditions prevents the dissolution of the polymer in low pH conditions. On the other hand, the ionization of the substituted phthalate groups permits the dissolution of the water-insoluble backbone of CAP in high pH conditions. These different mechanisms which control the dissolution of the polymer in different pH values apparently influence the dissolution rate of the polymer.

Between the polymers that have the same backbone structure, the degree of substitution contributes to different dissolution rates. One example is the two HPMCP polymers – HP-50 and HP-55. HP-50 has a lower proportion of phthalic acid groups (21-27%) than HP-55 (27-35%) (Koleng and McGinity, 2000), and thus dissolves at lower pH. In the above mentioned study by Davis et al. (1986a), the authors related the different dissolution rate of HP-50 and HP-55 to the different \( \text{pK}_a \) values of these two polymers. The lower dissolution pH threshold and faster dissolution rate at a given pH of HP-50 were due to the lower \( \text{pK}_a \) of the polymer (\( \text{pK}_a = 4.20 \)) compared to HP-55 (\( \text{pK}_a = 4.47 \)). The authors also pointed out that the determining factor of \( \text{pK}_a \) of the polymer is the distance separating the phthalate substituents in the polymer structure, which was related to the degree of substitution.
It was also reported in the literature that an increase in the degree of phthalyl substitution for different batches of PVAP increased the disintegration times of coated tablets (Delporte, 1970). Since the polyvinyl alcohol backbone of the polymer is water-soluble, the increased substitution of relatively hydrophobic phthalate groups was responsible for the decreased dissolution rate of the polymer.

The type of the substituents can also influence the dissolution properties of enteric polymers. This is exemplified by the lower dissolution pH of CAT (pH 5.0) compared to CAP (pH 6.0), due to the additional carboxylic acid in the substituent group of CAT. Having a water-insoluble backbone, the higher proportion of the ionizable carboxylic acid groups in the polymer structure allows CAT dissolving at a lower pH value.

### 1.3.3 Polymethacrylates

Polymethacrylates were first synthesized as organic glass with high tensile stress at break, hardness, and excellent stability in the early twentieth century. The pharmaceutical use of polymethacrylates as coating materials was developed by Röhm GmbH, Germany. Various polymethacrylate polymers are described under the brand name Eudragit® and used for different forms of coatings:

- Methacrylate aminoester copolymer (Eudragit® E) is a cationic polymer and suitable for coatings which dissolves in the acidic condition of the stomach.
- Methacrylate ester copolymers (Eudragit® RS, RL and NE) are designed as water insoluble, pH-independent polymers, which are insoluble in the digestive fluids of the entire GI tract, but have different degrees of permeability. These methacrylate ester copolymers are normally applied as diffusion-controlled coatings for sustained drug release.
• Methacrylic acid copolymer containing methacrylic acid, methyl acrylate, methyl methacrylate groups was newly developed known as Eudragit® FS, and is appropriate for colonic drug delivery.
• Methacrylic acid copolymers used for enteric coatings include poly(methacrylic acid, ethyl acrylate) -Eudragit® L 30 D-55/L 100-55 and poly(methacrylic acid, methyl methacrylate) -Eudragit® L 100/S 100.

Table 1.8 shows the chemical structures and solubility of methacrylic acid copolymers Eudragit® L 30 D-55/L 100-55, Eudragit® L 100 and Eudragit® S 100.

**Table 1.8. Chemical structure and solubility of methacrylic acid copolymers (Lehmann, 1989)**

<table>
<thead>
<tr>
<th>Polymer type</th>
<th>$n_1:n_2$</th>
<th>$R_1$</th>
<th>$R_2$</th>
<th>MW</th>
<th>Soluble at pH above</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eudragit® L 30 D-55/L 100-55</td>
<td>1:1</td>
<td>H</td>
<td>$C_2H_5$</td>
<td>250,000</td>
<td>5.5</td>
</tr>
<tr>
<td>Eudragit® L 100</td>
<td>1:1</td>
<td>$CH_3$</td>
<td>$CH_3$</td>
<td>135,000</td>
<td>6.0</td>
</tr>
<tr>
<td>Eudragit® S 100</td>
<td>1:2</td>
<td>$CH_3$</td>
<td>$CH_3$</td>
<td>135,000</td>
<td>7.0</td>
</tr>
</tbody>
</table>

These methacrylic acid copolymers are produced from emulsion polymerization as aqueous latex dispersions. Eudragit® L 30 D-55 is the original latex from emulsion
polymerization and commercially available as a dispersion, which could be directly applied as aqueous coating formulations with the addition of suitable plasticizers and glidants. The spray dried form of Eudragit® L 30 D-55 is available as powder - Eudragit® L 100-55, and can be used for organic solvent-based coating formulations or redispersed in water by adding small amounts of alkali. The redispersed pseudolatex of Eudragit® L 100-55 is comparable to the original latex dispersion (Eudragit® L 30 D-55) in terms of the particle size, gastric-resistance and dissolution properties in the small intestinal conditions (Lehmann, 1989).

Eudragit® L 100 and Eudragit® S 100 are also obtained by spray-drying the original latex and available as powder. The high content of carboxylic acid groups in the structure of Eudragit® L 30 D-55/L 100-55 and Eudragit® L 100 renders the low dissolving pH of these polymers and the suitability for use as enteric polymers targeting drugs to the proximal small intestine (Plaizier-Vercammen et al., 1992b; Felton et al., 1995; Dangel et al., 2000a; Dangel et al., 2000b; Bruce et al., 2003b). Of the two polymers, Eudragit® L 30 D-55/L 100-55 are more commonly used as enteric coatings than Eudragit® L 100 due to the lower dissolution pH threshold. The more hydrophobic polymer Eudragit® S 100, which has higher dissolving pH, is normally used for colonic drug delivery by applying the polymer alone or by mixing with Eudragit® L 100 or Eudragit® L 100-55 (Ashford et al., 1993b; Ashford et al., 1993a; Khan et al., 1999; Sinha et al., 2003; Bando and McGinity, 2006a; Bando and McGinity, 2006b; Ibekwe et al., 2006b).

1.3.4 Comparison of different enteric coatings

Enteric coating polymers are traditionally applied as organic systems. In recent years, aqueous coating systems have increasingly been preferred due to the safety, environment and economic concerns of organic solvent-based coatings. Methacrylic acid copolymers Eudragit® L 30 D-55 is commercially available as an aqueous dispersion. The spray dried powder –Eudragit® L 100-55 can also be used as
aqueous redispersion. However, most of the cellulose based enteric coatings and PVAP are still commonly utilized as organic systems, which limited their use. The only cellulose based enteric polymer that is recommended to be used as aqueous coatings is HPMCAS, commercially available as Aqoat® (Shin-Etsu Chemical Co. Ltd. Technical bulletin, 1998).

Great interest has been expressed in developing aqueous coating systems for other cellulose based polymers and PVAP. Some pseudolatex dispersions have been commercialized, such as Aquateric® (FMC, USA) made of CAP and Coateric® (Colorcon Ltd, UK) containing PVAP. However, the gastric-resistant properties of these aqueous coatings were reported to be less sufficient compared to the corresponding organic solvent systems (Chang, 1990; Bianchini et al., 1991; Schmidt and Niemann, 1992; Plaizier-Vercammen et al., 1992a; Garcia-Arieta et al., 1996; Thoma and Bechtold, 1999). It normally require larger or double amount of the polymer than the organic coating to protect the active substances in the simulated gastric fluids. In contrast, the aqueous latex dispersion of Eudragit® L 30 D-55 or the redispersion Eudragit® L 100-55 exhibited superior gastric-resistance compared to other aqueous enteric coatings (Chang, 1990; Plaizier-Vercammen and Van Molle, 1991; Bianchini et al., 1991; Schmidt and Niemann, 1992; Garcia-Arieta et al., 1996; Thoma and Bechtold, 1999). The necessary amount of coatings for sufficient protection in acid media is comparable to the organic system.

Comparing the two aqueous enteric coating systems Eudragit® L 30 D-55 and Aqoat®, Aqoat® has a relatively large particle size of 5 μm (Nagai et al., 1989), and thus the resultant film formation, drug release and storage stability are dependent on the formulation and processing parameters (Siepmann et al., 2006). In addition, to obtain a satisfactory gastric-resistance, it normally requires a curing process at elevated temperature and humidity. In comparison, the particle size of Eudragit® L 30 D-55 is 0.25 μm (Lehmann, 1989), which ensures easy film formation and particle coalescence, and no curing process is normally required.
A disadvantage for cellulose based polymers as enteric coatings, in general, is that, they are permeable to water vapour and gastric fluid. In one study, the permeability of enteric coatings to water vapour and simulated gastric fluid was compared, and CAP films were found to be more permeable than PVAP (Porter and Ridgway, 1981). The permeability of methacrylic acid copolymer films to water vapour is also low compared to cellulose based enteric polymers (Lehmann, 1989; Scheiffele et al., 1998).

Enteric coating polymers of an acid ester structure are susceptible to hydrolytic breakdown during storage. The hydrolysis results in the splitting off of the phthalic or acetic acids, and a consequent increase in the free acid content and decrease in the combined ester content. Thoma and Bechtold (1999) reported that the active ingredient pancreatin, which is an ester-cleaving component, induced the hydrolysis of HPMCAS. However, even without the influence of enzymes, the phthalic ester groups of HP-55 were partly cleaved after 11 months storage. Murthy et al. (1986) reported that CAP and PVAP coated hard gelatin capsules were unstable after long-term storage. Drug release in pH 6.8 buffer was delayed after storage in room temperature for nine months. The long-term stabilities of enteric-coated dosage forms coated with methacrylic acid copolymers were proved to be more satisfactory than other aqueous enteric coatings (Murthy et al., 1986; Bianchini et al., 1991; Thoma and Bechtold, 1999).

An important property of enteric polymers is the dissolution pH threshold, where the polymer starts to dissolve. As provided in Sections 1.3.3 and 1.3.4, enteric polymers designed to deliver drugs to the small intestine have dissolution pH threshold from 5.0-6.0. Theoretically, the lower the dissolving pH, the faster the polymer dissolves in small intestinal conditions. However, the dissolution pH threshold values of different enteric polymers are mainly provided by manufactures. In addition, the dissolution rate of the polymers at a given pH is also an important factor which
influences the performance of the final enteric coating. Although there are studies in which the dissolution rate of enteric polymers was compared at different pH values, different measurement methods and conditions were used (Spitaal and Kinget, 1977a; Davis et al., 1986a). Therefore, it is of value to directly compare the dissolution properties of currently used enteric polymers in same test conditions, and thus to gain a fundamental understanding of the in vitro and in vivo performance of enteric coatings.

1.4 IN VIVO/IN VITRO EVALUATION OF ENTERIC COATINGS

1.4.1 In vivo methods

Methods that are used to evaluate the in vivo performance of enteric-coated dosage forms include: imaging technique, pharmacokinetic study and the combination of these two. The most direct and commonly used imaging technique is γ-scintigraphy, which provides the time and position of the disintegration of enteric-coated products. The GI transit of dosage forms could be determined at the same time, and thus the gastric-resistance of the enteric-coated products can be assessed. In addition, the disintegration lag time post gastric emptying can be determined.

Pharmacokinetic study can also be used to analyse the drug absorption patterns from enteric-coated products. However, without the determination of the GI transit, the conventional pharmacokinetic results are not able to distinguish whether the delayed drug absorption is caused by the slow drug release from the coated products or the long gastric emptying time. Pharmacoscintigraphy, a combination of scintigraphy with pharmacokinetic studies, is then more advantageous by providing both the drug absorption profile and GI transit behaviour (Wilding et al., 2001). It also allows correlating the disintegration time to the onset appearance of drug in the plasma.
1.4.2 *In vitro* methods

*In vivo* methods are most reliable to evaluate enteric-coated products. However, for routine use such as quality control for batch manufacture and formulation development, it is not possible to repeatedly use human subjects. Therefore, for these purposes, *in vitro* evaluations are normally conducted, including the disintegration and dissolution test.

1.4.2.1 Disintegration test

The disintegration test is commonly required in pharmacopoeias to examine the gastric protection of enteric-coated products and the disintegration in subsequent buffer. The requirement of disintegration for enteric-coated tablets in British Pharmacopoeia (BP) and United States Pharmacopoeia (USP) are described as follows:

**BP (2006b)**

- *Acid stage*: in 0.1 M HCl (pH 1.2) for 2 hours, no tablet shows signs of cracks.
- *Buffer stage*: in mixed phosphate buffer (pH 6.8, 0.05 M), tablets disintegrate completely within 60 minutes.

**USP 27 (2006a)**

- *Acid stage*: in simulated gastric fluid (pH 1.2) for 1 hour, no tablet disintegration, cracking, or softening.
- *Buffer stage*: in simulated intestinal fluid (pH 6.8), tablets disintegrate completely within specified time under each monograph.
1.4.2.2 Dissolution test

Four types of dissolution apparatus are described in USP 27 (2006d) for testing solid dosage forms. These apparatus have also been adopted by the European Pharmacopoeia and the Japanese Pharmacopoeia, except USP apparatus III which is not accepted by the Japanese Pharmacopoeia.

- **USP apparatus I (basket apparatus) an apparatus II (paddle apparatus):** Both of these two apparatus utilize cylindrical vessels which contain the dissolution media. For apparatus I, the dosage form is placed in a mesh basket which is immersed in the vessel via a shaft, while, the basket is replace by a paddle in apparatus II and the dosage form is directly placed in the vessel. During the test, the shaft rotates at a pre-determined speed and gives the hydrodynamic movement of the media in the vessels. The volume of the media can be in the range of 250 to 2000 ml, but the most frequently used is 900 ml.

- **USP apparatus III (reciprocating cylinder):** This apparatus consists a series of glass reciprocating cylinders with stainless steel mesh at the top and bottom. The dosage form is contained in the cylinder and fitted in a set of flat-bottomed glass vessels with dissolution media inside. A device is used to allow the inner cylinder to reciprocate vertically inside the vessels at a selected rate. Media volumes of 200 to 300 ml are typically used.

- **USP apparatus IV (flow-through cell):** The dosage form is contained in a small volume cell. The dissolution media is continuously forced through the cell by a pump. The cell is mounted vertically with a filter system that prevents escape of undissolved particles from the top of the cell.
The vessels and cell for these four apparatus are immersed in a suitable water bath which holds the temperature of the media at 37 ± 0.5 °C. Compared to the others, the apparatus III is more practical in terms of media change. This can be achieved by containing different media in each row of the vessels, and thus is particularly useful for testing modified release dosage forms. The media in the apparatus IV can flow through in an “open loop”, which introduces fresh media continuously. This is particularly beneficial for drugs with low solubility. However, the apparatus I and II are still the most commonly used because of the well accepted standard and the comparability of the results between different research groups.

The dissolution test procedures for enteric-coated products are specified under delayed-release dosage forms in USP 27 (2006c), and can be applied with any of the above four apparatus. The interpretation for the test requirement is identical as in BP (2007):

- **Acid stage**: in 0.1 M HCl (pH 1.2) for 2 hours, no more than 10% drug released.
- **Buffer stage**: in sodium phosphate buffer (pH 6.8, 0.05 M), no less than 75% drug released within 45 minutes.

1.4.2.3 Similarity of the in vitro methods and in vivo conditions

The purpose of in vitro tests for enteric-coated products is mainly for quality control for batch manufacture. It is also used for formulation development. For both of these purposes, it is desirable for in vitro test methods to simulate the gastrointestinal conditions and thus predict the in vivo performance of the dosage forms. However, based on the knowledge of the gastrointestinal physiology, currently used in vitro methods do not adequately resemble in vivo conditions.
**Gastric-resistance test**

The gastric-resistance test does not take into account the gastric pH in the fed state and the reality of gastric emptying. As the gastric pH is in a range of 1.0-3.5 in fasted state, and increases up to pH 4.0-5.0 in the fed state (Malagelada et al., 1976; Ladas et al., 1983; Ovesen et al., 1986; Youngberg et al., 1987; Evans et al., 1988; Fallingborg et al., 1989; Dressman et al., 1990), such conditions are far removed from environment produced by the *in vitro* test medium of 0.1 M HCl (pH 1.2).

The standardised 1 or 2 hours *in vitro* gastric-resistance test dose not reflect the reality of gastric emptying. The gastric emptying of non-disintegrated dosage forms may vary significantly because of the different contents of the stomach and may take from less than 1 hour to up to 12 hours (Davis et al., 1988; Khosla and Davis, 1989; Coupe et al., 1991a; Ibekwe et al., 2006b).

Therefore, *in vitro* gastric-resistance tests at pH 1.2 for 1-2 hours could not possibly ensure the integrity of enteric-coated products in the stomach, if the gastric emptying of the product is delayed or the dosage form encounters high gastric pH conditions.

**Buffer test**

The currently used pH 6.8 *in vitro* disintegration or dissolution media do not adequately resemble any of these physiological factors of the small intestine luminal fluid:

**pH:**

The lumen pH of the proximal small intestine is not always as high as 6.8; it gradually increases from pH 5.0-6.0 to pH 6.5-7.0 (Rune and Viskum, 1969; Benn and Cooke, 1971; Ovesen et al., 1986; Fallingborg et al., 1989; Dressman et al.,
The main pH value of the duodenum was reported as around 5.5 in healthy volunteers in the period of 48 hours (Bratten and Jones, 2006).

**Volume:**

The volume of intestinal juice is far less than 900 ml as used in the most commonly applied *in vitro* tests (USP apparatus I and II). The total water content in the small intestine is 206 (60-352) ml (Gotch et al., 1957). The corresponding amount in the large intestine is 187 g (Cummings et al., 1990). In addition, the latest research demonstrates that the volumes of free fluid in the small intestine are just 105 ± 72 ml in the fasted state and 54 ± 41 ml after meal (Schiller et al., 2005). The fluid volume decreases further in the large intestine, with the free fluid of 13 ± 12 ml in the fasted and 11 ± 26 ml in the fed state.

**Ionic composition:**

The main dissimilarity of the ionic composition between the conventional phosphate buffer media from the luminal fluids is that, the luminal fluids are buffered by bicarbonate and the phosphate levels are very low. Furthermore, the presence of other ions in the luminal fluids contributes to a different ionic environment compared to the *in vitro* test media (Banwell et al., 1971; Lindahl et al., 1997; Fadda and Basit, 2005).

Based on the above understanding, the only *in vivo* condition that is resembled by the currently used compendial *in vitro* methods is the body temperature. Knowing the limitations of these *in vitro* test media, several attempts were reported in the literature to better simulate the small intestinal fluids, including the use of physiological bicarbonate buffer for testing either the dissolution of polymeric coatings or drug molecules (Chan et al., 2001; McNamara et al., 2003; Fadda and Basit, 2005). However, bicarbonate buffer encounters stability problems, especially at low pH values. The coordination of Dressman’s research group in Germany and Reppas’s group in Greece has intensively investigated the use of biorelevant
dissolution media to obtain a better understanding of the dissolution process in vivo (Galia et al., 1998; Dressman et al., 1998; Nicolaides et al., 1999; Lobenberg et al., 2000; Nicolaides et al., 2001; Kostewica et al., 2002). These biorelevant dissolution media include fasted state simulated intestinal fluid (FaSSIF) and fed state simulated intestinal fluid (FeSSIF). These media represent a simplification of the luminal composition, in terms of pH (6.5 for FaSSIF, and 5.0 for FeSSIF), osmolality, bile salt and lipid concentration. However, these media are buffered by either phosphate or acetate, instead of bicarbonate. In addition, the application emphasis of these biorelevant dissolution media is to predict the in vivo absorption of poorly soluble, lipophilic weak acids, weak bases and non-ionisable compounds, by probing the food effects (Dressman and Reppas, 2000).

Apart from the selection of representative media mimicking gastric and small intestinal conditions, another approach also considers the hydrodynamic and transit conditions of the GI tract, by using dynamic artificial gastrointestinal systems (TIM) (Blanquet et al., 2004). Two systems are designed for representing the human stomach and small intestine conditions (TIM-1) and colonic conditions (TIM-2). TIM-1 simulates the main parameters of digestion, including pH, peristaltic mixing and transit, salivary, gastric, biliary and pancreatic secretions. Although this system provides a comprehensive method to mimic the GI passage and successive conditions following the administration of a dosage form, there are practical issues with respect to the extended use of the TIM-1 system, such as the long preparation time and high costs.

1.5 IN VITRO/IN VIVO DISCREPANCY OF ENTERIC COATING PERFORMANCE

Since the currently used enteric polymers start to dissolve at relatively low pH values (pH 5.0-6.0), it is commonly believed that enteric-coated dosage forms,
coated with these low dissolution pH threshold polymers, rapidly disintegrate after gastric emptying and on entry into the small intestine; however, this is not the case.

For dosage forms coated with low dissolution pH threshold polymers such as CAP, HPMCP and Eudragit® L 30 D-55/L 100-55, \textit{in vitro} disintegration always occurs rapidly, normally within few minutes in simulated intestinal pH conditions (see Table 1.9). In addition, the \textit{in vitro} dissolution of enteric-coated products normally complies the official requirement that greater than 75% of the drug released within 45 minutes, and in most cases the dissolution time is much shorter than this (Bianchini et al., 1991; Garcia-Arieta et al., 1996; Lehmann et al., 1997; Dangel et al., 2000a; Bruce et al., 2003b). However, numerous \textit{in vivo} studies utilizing imaging techniques such as gamma sntigraphy have shown that it can take up to 2 hours for enteric-coated products to disintegrate after gastric emptying (Table 1.9).

The combination of standard pharmacokinetics with gamma sntigraphy studies has also been applied to assess the \textit{in vivo} performance of enteric coatings. Basit et al. (2004) investigated the gastric residence time and plasma concentration data of PVAP coated ranitidine pellets. Their study established that the mean gastric residence time of enteric-coated pellets was 0.8 hours; however, the time for first appearance of ranitidine in plasma was 1.4 hours. Furthermore, the time to reach peak plasma concentration ($T_{\text{max}}$) was significantly longer for enteric-coated pellets compared to the uncoated pellets: 4.1 and 2.9 hours, respectively.

Gordon et al. (1995) investigated the pharmacokinetics of naproxen sodium tablets coated with CAP, CAT, CAP/CAT (50:50), and methacrylic acid copolymer respectively. \textit{In vitro} dissolution testing showed that all of the enteric-coated tablets completely dissolved within 45 min in the pH 7.4 phosphate buffer. However, the \textit{in vivo} $T_{\text{max}}$ values were significantly longer for CAP, CAP/CAT (50:50), and methacrylic acid copolymer coated tablets (2.3, 2.2, and 2.6 hours respectively) compared to the uncoated tablet (1.1 hours). The $T_{\text{max}}$ of the CAT formulation (1.5
hours) was significantly faster than the other three enteric formulations and was statistically similar ($p = 0.130$) to the uncoated tablet formulation. However, since the authors did not carry out a gamma scintigraphy study, it is not clear whether the CAT formulation disintegrated in the upper small intestine or failed to protect the integrity of the tablets in the stomach.

**Table 1.9. In vitro and in vivo disintegration time of some enteric-coated dosage forms**

<table>
<thead>
<tr>
<th>Dosage forms</th>
<th>In vitro disintegration time in pH 6.8 phosphate buffer</th>
<th>In vivo disintegration time after gastric emptying, mean (± SD)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eudragit® L 30 D-55 coated capsules</td>
<td>-</td>
<td>1.6 (± 0.9) hour</td>
<td>(Cole et al., 2002)</td>
</tr>
<tr>
<td>Eudragit® L 30 D-55 coated tablets</td>
<td>9 minutes</td>
<td>Started on 38 (± 15) minutes; completed on 10 (± 6) minutes later</td>
<td>(Lehmann et al., 1997)</td>
</tr>
<tr>
<td>Eudragit® L 100 coated pellets</td>
<td>-</td>
<td>1.97 (± 0.55) hour</td>
<td>(Ebel et al., 1993)</td>
</tr>
<tr>
<td>methacrylic acid copolymer* coated tablets</td>
<td>&lt; 30 minutes</td>
<td>93 (range, 11-134) minutes in fasted state; 85 (range, 27-140) minutes in fed state.</td>
<td>(Wilding et al., 1992)</td>
</tr>
<tr>
<td>Aqueous acrylic resin dispersion coated tablets</td>
<td>-</td>
<td>1.2 (range, 0.1-2.1) hours</td>
<td>(Hardy et al., 1987)</td>
</tr>
<tr>
<td>CAP coated capsules</td>
<td>10 minutes</td>
<td>155 (± 63.2) minutes</td>
<td>(Catteau et al., 1994)</td>
</tr>
<tr>
<td>CAP coated tablets</td>
<td>-</td>
<td>20 - 110 minutes</td>
<td>(Bogentoft et al., 1984)</td>
</tr>
<tr>
<td>CAP coated capsules</td>
<td>&lt; 20 minutes</td>
<td>95 (± 33) minutes in fasted state; 66 (± 28) minutes in fed state.</td>
<td>(Kenyon et al., 1994)</td>
</tr>
<tr>
<td>Aqueous based enteric-coat designed to dissolve at pH 4.5-5.0 (tablets)</td>
<td>-</td>
<td>More than 80 minutes</td>
<td>(Wilding et al., 1993)</td>
</tr>
</tbody>
</table>

*: Coating formulation using the standard coating solution as the marketed Naprosyn EC formulation which contains methacrylic acid copolymer with rapid dissolution at pH above 6.
These *in vivo* study results obtained from the newly developed and currently used enteric polymers, thus, demonstrate that enteric-coated products disintegrate and release active substance after significant lag times in the human small intestine. In addition, there is still a major discrepancy between *in vitro* disintegration/dissolution data and *in vivo* performance of enteric-coated dosage forms. From the established dissimilarity of the *in vitro* testing methods to the *in vivo* conditions, the existence of this discrepancy is not surprising.

### 1.6 CLINICAL IMPLICATIONS OF DELAYED DRUG RELEASE FROM ENTERIC-COATED DOSAGE FORMS

As highlighted above, enteric-coated products can take up to 2 hours to disintegrate post gastric emptying. As small intestinal transit time is of the order of 3-4 hours (Davis et al., 1986b), disintegration and drug release from such enteric-coated dosage forms will occur in the distal small intestine. Such delay of drug release can have undesired clinical implications, including: ineffective drug therapy; decreased bioavailability for drugs with an absorption window in the proximal small intestine and delayed onset of action.

As an example, pancreatic enzyme supplements - accepted as the primary approach to treat pancreatic insufficiency of those patients with cystic fibrosis - are commonly applied as enteric-coated products to prevent enzyme degradation in the stomach. However, inefficient enzyme function using enteric-coated formulations has been reported and related to the failure or delayed enzyme release from enteric-coated preparations (Marotta et al., 1989; Robinson et al., 1990; Guarner et al., 1993). The delayed release causes the loss of the available contact time between chyme and enzymes, leading to an insufficient enzyme effect. In addition, lower duodenal pH values were found in cystic fibrosis patients compared to healthy people, which further retards the disintegration and dissolution of enteric-coated formulations.
based on pH-dependent coating polymers (Youngberg et al., 1987; Robinson et al., 1990). In some research results, enteric-coated enzyme supplements were even less effective than non-coated products (Marotta et al., 1989). To overcome this drawback of conventional enteric-coated tablets, enteric-coated microsphere pancreatic enzyme preparations were developed and proved to be more efficient due to the fast release of enzymes in the duodenum (Littlewood et al., 1988). However, it is conceivable that enteric-coated tablets which can provide comparable fast release to microspheres, would be preferred due to the simpler manufacturing process and lower cost of production.

The ineffective drug therapy caused by the delayed drug release from enteric-coated dosage forms can also be due to the insufficient drug absorption and the resulting low bioavailability for those drugs having the optimum site of absorption in the upper part of the small intestine. Levodopa was commonly applied as enteric-coated preparations to overcome the gastric side effect; however, the intestinal absorption of levodopa is mainly in the upper small intestine (Gundert-Remy et al., 1983). It has been proven that the bioavailability of levodopa could be improved by loading high concentrations of the drug at the proximal small intestine (Nishimura et al., 1984). Other drugs such as acetylsalicylic acid and pyridoxal phosphate were also shown to achieve higher bioavailability from enteric-coated formulations with faster drug release (Lappas and McKeehan, 1967; Kaniwa et al., 1985; Torrado et al., 1996).

In cases where rapid onset of action is preferred, it would be of importance to release the active drug substances as quickly as possible. This has obvious impact on the treatment of acute pain, for example postoperative dental pain or in painful osteoarthrosis. Delayed drug release from conventional enteric-coated nonsteroidal anti-inflammatory drugs such as diclofenac is undesired in relief of acute pain. In these cases, dispersible tablets are believed to be preferred in terms of rapid onset
time. However, dispersible tablets showed more frequent and severe GI side-effects than enteric-coated tablets (Bakshi et al., 1993).

It has also been noted that the absorption of oral proton-pump inhibitors (PPIs) is delayed by the enteric coating required to protect the acid-labile drugs from degradation in the stomach, resulting in the delayed antisecretory effect. A new strategy of delivering PPIs to the GI tract has been developed using immediate-release formulations. Immediate-release omeprazole/sodium bicarbonate oral suspension and capsule (ZGERID®) have been proved by FDA and launched on the market in 2004 (CDER Drug and Biologic Approvals for Calendar Year 2004, FDA). These immediate-release omeprazole formulations have a higher mean peak plasma omeprazole concentration ($C_{\text{max}}$) and a significantly shorter mean time to reach $C_{\text{max}}$ ($T_{\text{max}}$) than enteric-coated omeprazole (Howden, 2005).

Similar results were obtained with didanosine formulations which showed better pharmacokinetic profiles with didanosine immediate-release buffered tablets compared to the enteric-coated tablets and beads. The $T_{\text{max}}$ of enteric-coated didanosine beads and mini-tablets are significantly longer than buffered tablets, with the values of 1.33, 2.83 and 0.67 hours respectively (see Figure 1.6) (Damle et al., 2002b).

However, despite that immediate-release formulations are superior to enteric-coated formulations in terms of rapid onset time, the dispersible tablets do not solve the problem of gastric side-effects in the case of nonsteroidal anti-inflammatory drugs and the antacid buffer used in the buffered formulations can cause stomach upsets and influence the absorption of other medication taken at the same time. Therefore, enteric-coated products which dissolves rapidly in the small intestine and provide comparable onset time to immediate release formulations would be preferred.
1.7 POTENTIAL STRATEGIES FOR ACCELERATING THE DISSOLUTION OF CONVENTIONAL ENTERIC COATINGS

As above discussed, the significantly delayed drug release from conventional enteric-coated products in the human small intestine has clinical implications. Chemical approaches or formulation approaches are potential strategies to obtain rapid release enteric coatings.

1.7.1 Chemical approaches

Development of novel enteric coating agents soluble at more acidic pH than conventional enteric polymers can possibly increase the dissolution rate of enteric coatings in small intestinal conditions. This can be achieved using chemical approaches, by either designing new enteric polymer entities or modifying currently available polymers.

To our knowledge so far, the design of new pH-dependent enteric polymers other than cellulose, polyvinyl and methacrylate backbones has not been reported.
However, the possibility of modifying existing enteric polymers to achieve low dissolution pH threshold has been investigated. In an attempt, HPMCP was modified with trimellitic acid, and the dissolution pH of the obtained polymer was controlled in the range of pH 3.5-4.5 (Kokubo et al., 1997). This is achieved by varying the content of trimellityl groups and the methoxyl substitution of the base polymer.

A similar approach was also applied for modifying other pH-dependent enteric polymers to alter the dissolution pH, yet for targeting to the colon. Modification of Eudragit® S to achieve different dissolution pH profiles has been described by Peeters and Kinget (1993). The dissolution pH of Eudragit® S was shifted to higher levels by forming methyl derivatives of the polymer. This is potentially advantageous to deliver active substances to the colon.

Various possibilities can be exploited for chemically modifying enteric polymers to achieve different dissolution pH and rapid release. This can be demonstrated by significant progress in chemical modification of polymers to achieve specific drug delivery purposes.

One fascinating example is the development of cellulose ethers. As a chemical raw material, cellulose has been used for about 150 years, and is considered an inexhaustible source for developing pharmaceutical excipients. The majority of cellulose derivates are cellulose ethers prepared by etherification of hydroxyl groups. The well established and widespread used cellulose ethers include hypromellose (HPMC), methylcellulose (MC), hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), ethyl cellulose (EC) and sodium carboxymethyl cellulose (SCMC). The solubility and thermal properties of these cellulose ethers are controlled by the constitution of the ether groups, the degree of substitution and the distribution of substituents. The various choices of properties and the biological compatibility of cellulose derivatives make them very popular in both the
application of conventional pharmaceutical dosage forms and the design of controlled delivery dosage forms.

Various other polymers are subjected to chemical modifications to overcome the limitations of the polymer and achieve desired properties for drug delivery. Particular attention has been drawn to natural polysaccharides such as chitosan, gellan gum, guar gum, xanthan gum, pectin, alginates and dextrans. One example gives the modification of dextrans to form pH-dependent hydrogels. Dextrans are produced by bacteria from sucrose or by chemical synthesis. Structurally dextrans consist predominantly of linear $\alpha-1, 6$-glucosidic linkage with some degree of branching via $\alpha-1, 3$-linkage. The limitation of dextrans for modified drug delivery is the very high water solubility. This can be overcome by forming dextran hydrogels capable of undergoing pH-responsive swelling. These hydrogels were obtained by cross-linking dextran with different materials such as 1, 10-diaminodecane, maleic acid and acrylic acid (Kim et al., 1999; Chiu et al., 1999; Chiu et al., 2002). The magnitude of swelling of dextran-maleic acid (Dex-MA) hydrogels were highly dependant on the pH of the medium (Kim et al., 1999). The highest swelling ratio occurred in neutral pH, followed by acidic pH (pH 3).

Another captivating area of polymer modification is the design of responsive polymeric delivery systems. These systems based on the use of so called “smart” polymeric materials- hydrogels undergoing dramatic property changes in response to different stimuli. These stimuli can be both external and internal to the body, including: temperature, pH, ionic composition, light, electric and magnetic field.

The stimuli-responsive properties of hydrogels can be obtained by chemically introducing functional groups to the constituent polymer structure. One example is the incorporation of superparamagnetic iron oxide ($\text{Fe}_3\text{O}_4$) into polymeric systems to obtain magnetically-responsive materials. In one study, $\text{Fe}_3\text{O}_4$ particles were
incorporated into polymerized liposomes so that the liposomes became magnetically responsive (Chen and Langer, 1997). Both magnetic- and thermo-sensitive hydrogel nanocomposites can also be synthesized by loading Fe$_3$O$_4$ into thermo-responsive poly(N-isopropylacrylamide) structure (Satarkar and Hilt, 2007). The drug release from such nanocomposite hydrogels can be remote-controlled by utilizing an alternating high-frequency magnetic field. The magnetic field can lead to heat generation, which can drive the swelling transition of the hydrogel.

From the above demonstration of chemically modifying polymers to achieve desired properties, one can deduce that there is a potential of using chemical approaches to achieve rapid release enteric coatings. However, two problems arise by such chemical modification.

Firstly, the strategy of decreasing the polymer dissolution pH could be problematic, considering the reality of gastric pH. The fasted gastric pH lies in the range of 1.0-3.5 (Ovesen et al., 1986; Evans et al., 1988; Fallingborg et al., 1989; Dressman et al., 1990), and can be higher in elderly subjects and patients with gastric disease (Gardham and Hobsley, 1970; Russell et al., 1993). More importantly, the intragastric pH value increases up to 4.0-5.0 after a meal and takes 1-2 hours to return to the fasted pH (Malagelada et al., 1976; Ladas et al., 1983; Dressman et al., 1990). Enteric coatings which dissolve at pH below 5.0 can be risky to maintain integrity in the stomach for patients with high fasted gastric pH or in fed state.

Secondly, chemical alteration of the polymer will lead to the formation of new chemical entities, which could change the intrinsic properties of the polymer, especially the toxicological profiles. This can be exemplified by the application of azo-polymers for colonic delivery. The use of synthetic polymers cross-linked with azo-aromatic groups as coatings to deliver insulin and other peptide drugs to the colon has been pioneered by Saffran and co-workers (1986). The azo-bonds of the polymer are susceptible to the cleavage of the colonic bacteria. This azo-reduction
can break the cross-links of the polymer, and thus degrade the polymer films. The loaded drug can then be released to the lumen of the colon for local action or for absorption. However, although the evaluation of this delivery system has been conducted in experimental animals, further \textit{in vivo} studies in human has been held back, due to the azo toxicity-related problems (Mooter et al., 1997). Synthetic azo-aromatic compounds are potential carcinogens, which requires further safety/toxicity evaluations (Basit, 2005).

1.7.2 Formulation approaches

Apart from chemical approaches of designing new enteric polymers or modifying the existed polymers for rapid dissolution in the small intestine, formulation approaches can also be used for this purpose.

To achieve fast dissolution of enteric coatings in the small intestine, the potential formulation strategies could be the incorporation of components in the film coat, thus assisting its dissolution in small intestinal conditions but remaining intact in the stomach. The selection of such components can be based on exploring the physiological differences between the stomach and the small intestine. These differences have been highlighted in details in Section 1.2, and mainly focus on the differences of ionic composition and pH.

Among these physiological differences between the stomach and the small intestine, the pH difference is the most significant and also the basis of the currently used enteric polymers. Materials which have properties sensitive to pH changes are potentially useful to assist the dissolution of enteric coatings at elevated pH.

Low molecular weight organic acids are unionizable in low pH medium such as 0.1 M HCl, and have low solubilities. However, these acids are fully ionized in high pH medium such as pH 6.8 buffer, thus having higher solubilities than in acidic
conditions (Pearnchob et al., 2004). On incorporating these organic acids into enteric coatings, they can remain in the coat in low pH, but dissolve and leach in high pH conditions. This can possibly result in good gastric resistance and rapid disintegration of the coat in the small intestinal fluids.

Besides the low molecular weight organic acids, high molecular weight polymers such as pectin, alginates and xanthan gum also have pH-sensitive properties. These polymers are anionic polymers with carboxylic groups in the structure, which are un-ionizable below and ionizable above the pK_a. In low pH conditions, these anionic polymers remain intact. However, in high pH conditions, since the ionization of acidic groups, the polymer chains repel each other and thus absorb surrounding medium into the polymer structure and swell to a large extension. If including these polymers into enteric coatings, the pH-sensitive swelling property can possibly render them the potential ability to remain in the coat in low pH conditions of the stomach and swell in high pH conditions of the small intestine. The dissolution of the enteric coatings in high pH conditions can presumably be accelerated by the promotion of the medium uptake due to the swelling of the pH-sensitive polymers.

Compared to chemical approaches, modification of enteric coatings with formulation approaches could prevent the toxicity problems by selecting additive compounds with well known safety, and would not be subject to the same stringent regulation as new polymer. In addition, by modifying enteric coating formulations, it is possible to develop enteric coatings with fast dissolution in small intestinal conditions and without decreasing the dissolution pH threshold of the polymer. This can prevent the compromise of the acid-resistance of the coat in extreme gastric pH conditions.

In the present study, formulation approaches were applied to accelerate the dissolution of enteric polymer coatings. The potential of incorporating pH-sensitive materials into enteric coatings for this purpose were explored. A novel enteric
coating system with two coating layers (double coating) was designed based on the study with pH-sensitive materials. The possibility of applying this double coating enteric system for rapid dissolution and drug release in conditions simulating the upper small intestine was investigated.

1.8 SCOPE AND PURPOSE OF STUDY

To overcome the limitations of conventional enteric coatings due to delayed drug release, it is necessary to accelerate the dissolution of enteric polymer coatings in small intestinal conditions. The aims of this work are:

- To explore the influences of incorporating organic acids and pH-sensitive polymers in enteric polymer free films on their dissolution properties. To understand these influences through the investigation of the physicochemical properties of the films.

- To evaluate the potential of a novel double-coated system on accelerating the dissolution of enteric coatings by comparing its drug release profiles and polymer dissolution velocities with a conventional enteric coating. To gain insight of the coat dissolution mechanisms of the double coating system through the revelation of the coat dissolution processes. To optimize the double coating system.

- To achieve a fundamental understanding of the mechanisms involved in the dissolution of the double coating system by identifying the roles of inner coat properties on the dissolution. These properties include the inner coat composition, ionic strength, buffer capacity and osmotic pressure. To establish the assistance of inner coat in the outer coat dissolution by investigating the migration of ions from the inner to the outer coat.
CHAPTER 2

EFFECTS OF pH-SENSITIVE MATERIALS ON ENTERIC POLYMER FILM DISSOLUTION
2.1 INTRODUCTION

2.1.1 The use of pH-sensitive materials for accelerating enteric coating dissolution

Chapter 1 highlighted the necessity for modifying conventional enteric coatings to achieve rapid dissolution and drug release in the proximal small intestine. Instead of chemically changing the enteric polymer which would fundamentally alter the polymer properties and is subject to regulation requirements, formulation approaches are more conceivable and feasible for this purpose. The potential strategies include introducing materials in the enteric film coat to assist its dissolution in the small intestine while maintaining its gastric-resistant properties. Physiological differences between the stomach and the small intestine, which have been illustrated in Chapter 1, provide useful guides for selecting the potential materials.

The pH difference between the stomach and the small intestine is one of the most apparent and substantial features of the GI tract. This imparts the possibility of including pH-sensitive components in enteric coatings. Components having pH-sensitive properties could be divided into two types based on their molecular weight: low molecular weight components, such as organic acid; and high molecular weight components, such as pH-sensitive polymers. Low molecular weight organic acids exhibit pH-dependant solubility, while the swelling properties of high molecular weight pH-sensitive polymers are susceptible to pH changes. Both properties render these materials with the potential to assist in the enteric coat dissolution in the small intestine without compromising its gastric-resistance. The use of organic acids and pH-sensitive polymers in enteric films for rapid dissolution in small intestinal conditions is investigated in this chapter.
2.1.2 The use of free films for investigating coating formulations

In this phase of the study, free polymeric films are used to investigate coating formulations. In the literatures, there are numerous studies whereby free films are applied to develop film coating formulations. One reason for the use of free films is that their preparation is more efficient than applying coating formulations on tablet or pellet cores. More importantly, testing the properties of free films could predict the performance of the film coatings on the final coated products. The glass transition temperature ($T_g$), minimum film-forming temperature and the mechanical properties of free films can lead to an understanding of the film formation process on substrates and thus are of particular importance for optimizing the coating conditions. Since these film properties are mainly affected by the additives in the film such as plasticizers and fillers (Gutierrez and McGinity, 1994; Heinamaki et al., 1994b; Wu and McGinity, 1999; Qussi and Suess, 2006), they are also important for optimizing film formulations. Furthermore, the film permeabilities to oxygen, water vapour, hydrochloric acid and active substances, along with their solubility and dissolution rates provide prediction of stability and drug release from film coated dosage forms. However, to better predict the performance of film coated products using free films, the similarity of these two is of importance. This requires an understanding of the film formation mechanisms of polymeric film coatings and thus to better simulate the film formation of the actual coating by the preparation method of free films.

2.1.2.1 Mechanisms of film formation

The film formation mechanisms of polymeric film coatings could be very different depending on the use of polymer solution or dispersion. Organic solutions were traditionally used for film coatings; however, problems associated with organic solvents with respect to environmental and economic concerns limited their usage. Aqueous polymeric dispersions have therefore been introduced to overcome the
shortcomings of organic film coating systems. Commercially available aqueous colloidal dispersions could be divided into latex and pseudolatex dispersions. The latex dispersions are prepared by emulsion polymerization, while pseudolatexes are prepared by emulsifying the previously polymerized monomers or suspending spray-dried or mechanically milled solid polymeric particles.

Film formation from organic polymer solutions is initiated by the fast evaporation of the organic solvent and the increasing concentration of the polymer in the solution, which eventually leads to the formation of gel. After further loss of solvent, a continuous polymeric film is obtained.

Film formation from aqueous dispersion is more complex due to the involvement of the coalescence of polymeric particles to form a continuous film. The theory of film formation from aqueous polymer dispersions has been described in the literature since the 1950s. Figure 2.1 demonstrates the film formation process from a latex dispersion. This process was divided by Vanderhoff (1973) into three stages: (i) in the first stage, water evaporates from the bulk dispersion and the polymer particles can move between each other; (ii) the second stage starts when the solid concentration increases to a certain point and the particles come into irreversible contact with one another, and water evaporates through the interstices between the polymer particles; (iii) the third stage begins with the deformation and coalescence of the particles, and after the remaining water evaporates by diffusion, a continuous dry film is obtained.
From the second stage to the third stage, there are driving forces to promote the particle deformation and complete coalescence, as shown in Figure 2.2. In the 1950s, the driving forces were described as the polymer-water interfacial surface tension (Dillon et al., 1951) or the capillary force (Brown, 1956), both arising as the result of water loss. Later researchers pointed out that the surface tension or capillary force alone is insufficient to overcome the hinder forces and to cause the complete coalescence. The permanent particle deformation is the result of the combination of capillary and interfacial forces (Vanderhoff et al., 1966; Eckersley and Rudin, 1990).

Figure 2.1. Mechanism of film formation from aqueous dispersion. Reproduced from Hogan (1995).
2.1.2.2 Cast vs sprayed films

The properties of film coatings obtained from organic solution are mainly determined by the chemical and structural properties of the polymer. However, the coating process conditions have profound impact on the properties of films deposited on the substrate from aqueous dispersions, due to the complex nature of film formation (Yang and Ghebre-Sellassie, 1990; Lorck et al., 1997; Petereit and Weisbrod, 1999). Therefore, the preparation technique of free films is critical to better simulate the actual film formation process from aqueous dispersions. Free films could be prepared by either casting or spraying the solution or dispersion onto polished surfaces such as Teflon plates. For the same film formulation, films obtained from spraying and casting technique exhibit different properties such as appearance, mechanical properties and permeability (Allen et al., 1972; Spitael and
Kinget, 1977b; Obara and McGinity, 1994; Obara and McGinity, 1995; Sun et al., 1999). Between these two methods, the spraying technique is considered to be more advantageous in terms of better mimicking the real coating conditions, especially for coating formulations based on aqueous dispersions. Furthermore, the polymeric particles in the aqueous dispersion tend to settle during the drying process in the cast method, which will lead to uneven film formation.

Despite the advantages of the spraying method, preparing free films using this technique involves the use of complicated and special apparatus which normally includes a spraying system, a rotary drum or cylinder and a temperature control. In addition, the resultant film properties from spray and cast method are not always different. It has been reported in the literature that the mechanical properties of free films prepared from Eudragit® L 30 D-55 (aqueous) and Eudragit® L 100-55 (organic) were independent of the processing variables of the spraying technique (Obara and McGinity, 1995). It was also reported that the properties of spray films from Eudragit® L 30 D-55 did not significantly differ from those of the cast films (Obara and McGinity, 1994). Films formed from this polymeric dispersion had a minimum film-forming temperature lower than room temperature (< 23 °C), and the particles in the latex dispersion had relatively small size (the mean particle size of 0.2 μm) (Lehmann, 1989). These properties of the dispersion provide easy particle coalescence during film formation, and ensure the particles in the dispersion to remain stable for long periods during film casting. In the present study, free films of enteric polymers were prepared using casting method.

2.1.3 Model enteric coatings used in the study

Methacrylic acid ethyl acrylate copolymer Eudragit® L 30 D-55 and Eudragit® L 100-55 were used as model enteric coatings for this study. Among the enteric polymers, Eudragit® L 30 D-55/L 100-55 has gained the largest market share and scientific interest after being introduced to the market in 1970s. The advantages of
Eudragit® L 30 D-55/L 100-55 over other enteric coating polymers include the availability of aqueous formulations, good gastric-resistance, low water vapour permeability and satisfactory long-term stability, as discussed in Chapter 1.

Eudragit® L 30 D-55 is obtained from emulsion polymerization as aqueous latex dispersion. Eudragit® L 100-55 is the spray dried powder of Eudragit® L 30 D-55 and can be used as organic solution or redispersed in water. The chemical structure of Eudragit® L 30 D-55/L 100-55 is given in Chapter 1. Table 2.1 lists some fundamental information on Eudragit® L 30 D-55 and Eudragit® L 100-55.

<table>
<thead>
<tr>
<th>Chemical name</th>
<th>Eudragit® L 30 D-55</th>
<th>Eudragit® L 100-55</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular Weight</td>
<td>250,000</td>
<td>250,000</td>
</tr>
<tr>
<td>$pK_a$ of the methacrylic acid monomer</td>
<td>4.6</td>
<td>4.6</td>
</tr>
<tr>
<td>Dissolution pH threshold</td>
<td>5.5</td>
<td>5.5</td>
</tr>
<tr>
<td>Acid value**</td>
<td>Equivalent to 300-330 mg KOH/1 g polymer</td>
<td>Equivalent to 300-330 mg KOH/1 g polymer</td>
</tr>
<tr>
<td>Availability</td>
<td>Aqueous dispersion with 30% solid content</td>
<td>Powder</td>
</tr>
<tr>
<td>Particle size</td>
<td>0.2 μm</td>
<td>0.2 μm</td>
</tr>
<tr>
<td>pH of the dispersion</td>
<td>3.0-3.3 (slightly variable between batches)</td>
<td>-</td>
</tr>
</tbody>
</table>

* Reference: (Lehmann, 1989)
SECTION 1: THE USE OF ORGANIC ACIDS IN ENTERIC POLYMER FILMS

2.2 INTRODUCTION

It has been discussed in Chapter 1 that some of the low molecular weight organic acids have pH-sensitive water solubility. These acids are unionizable in low pH conditions and ionizable in high pH conditions, thus showing low water solubility at low pH and high water solubility at high pH. It was hypothesized that by including these organic acids in enteric films, the pH-sensitive solubility of these acids would allow the acids to remain in the film in acid medium and assist in the film dissolution in buffer. Some of the organic acids, such as sorbic acid, benzoic acid, fumaric acid and adipic acid, have significant solubility difference between pH 1.2 HCl and pH 6.8 phosphate buffer. This has been reported in the literature (Peamchob et al., 2004). Therefore, these acids would be desirable to achieve acid-resistance and fast dissolution in buffer. For example, sorbic acid has been proved to effectively assist the dissolution of shellac film in simulated intestinal fluids (Peamchob et al., 2004).

Other organic acids, such as citric acid, have high solubility at both low and high pH conditions. It is possible that using these organic acids in enteric coatings can compromise the acid-resistant ability of the coat due to the high solubility in acid medium. However, the general high water solubility of these acids would still be advantageous for the fast film dissolution in buffer. Table 2.2 provides chemical formulation, molecular weight and pK<sub>a</sub> value of some organic acids.
<table>
<thead>
<tr>
<th>Name</th>
<th>pKₐ</th>
<th>Formulation</th>
<th>Molecular Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorbic acid</td>
<td>4.76</td>
<td>C₆H₅O₂</td>
<td>112.13</td>
</tr>
<tr>
<td>Benzoic acid</td>
<td>4.2</td>
<td>C₇H₆O₂</td>
<td>122.12</td>
</tr>
<tr>
<td>Fumaric acid</td>
<td>3.02</td>
<td>C₄H₄O₄</td>
<td>116.07</td>
</tr>
<tr>
<td></td>
<td>4.38</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adipic acid</td>
<td>4.41</td>
<td>C₆H₁₀O₄</td>
<td>146.14</td>
</tr>
<tr>
<td></td>
<td>5.41</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Succinic acid</td>
<td>4.21</td>
<td>C₄H₆O₂</td>
<td>118.09</td>
</tr>
<tr>
<td></td>
<td>3.13</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4.76</td>
<td>C₆H₅O₇</td>
<td>192.13</td>
</tr>
<tr>
<td></td>
<td>6.4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The use of organic acids as pharmaceutical excipients has been well documented in the literature. The main area of application is to modify drug release from film coated or matrix formulations. Narisawa et al. (1994; 1996) have reported a sigmoidal release system comprising an organic acid-containing drug-loaded pellet core and a water insoluble Eudragit® RS coat. The organic acid in the core can increase the permeability of the Eudragit® RS coating by electrostatic interaction with the quaternary ammonium group of the polymer, and a rapid release of active drug after a predetermined lag time could be achieved. In another study, enteric-coated matrix granules using enteric polymer both as binder and coating material were formulated into enteric-coated tablets (Nykanen et al., 1999; Nykanen et al., 2001). Organic acids (e.g. citric acid) were added into the tablet matrix. Drug release from the tablets was delayed by the decreased microenvironment pH for the enteric polymer to dissolve due to the presence of the organic acid. Such system with delayed drug release is suitable for drug targeting to the colon.
Another colon-targeted delivery system was also designed based on the inclusion of organic acid in the formulation, yet a different approach was used (Ishibashi et al., 1998). The system contained an organic acid and an active ingredient in a capsule coated with a three-layered film. From the core to the outer coat, the film consists of an acid-soluble polymer, a water-soluble polymer and an enteric polymer. Drug release was prevented in the stomach due to the acid-resistance of the outer enteric coating. After gastric emptying, the outer layer and the intermediate water soluble layer dissolved. The acid soluble inner layer consisting Eudragit® E as the coating polymer was insoluble in high pH conditions of the small intestine. However, when the micro-environmental pH inside the capsule gradually decreased due to the dissolution of the organic acid, the inner layer was dissolved by the acidic fluid, and the drug content was quickly released.

Organic acids have also been included in sustained-release matrix tablets to achieve pH-independent release of weakly basic drugs (Streubel et al., 2000). The pH-dependent solubility of a weakly basic drug could lead to in vivo variability and bioavailability problems when applied as sustained-release dosage forms. The problem could be overcome by the inclusion of organic acids in matrix tablets to maintain an acidic milieu for pH-independent drug release. A similar concept was applied for sustained-release of weakly basic drugs from dosage forms coated with a diffusion layer (Thoma and Zimmer, 1990). Precipitation of the basic drug under high pH conditions of the small intestine was prevented by inclusion of organic acid in the core, and thus pH-independent drug diffusion through the film coating was achieved.

The aim of this section of the study was to investigate the effects of incorporating organic acids in Eudragit® L 30 D-55 and Eudragit® L 100-55 films on dissolution properties of cast free films. Organic acids with both low and high water solubility were investigated. The dissolution properties of the film were evaluated in acid
medium and buffer solutions, through determination of their acid/buffer uptake and weight loss in these test media.

2.3 MATERIALS

Eudragit® L 100-55 and Eudragit® L 30D-55 were donated by Röhm GmbH, Darmstadt, Germany. Triethyl citrate (TEC) was purchased from Lancaster Synthesis, Lancashire, UK. Sorbic acid, fumaric acid, benzoic acid, adipic acid, citric acid and succinic acid were purchased from Sigma, St. Louis, MO, USA. All the salts used to prepare the buffers and 5 M HCl were of analytical grade and obtained from VWR International Ltd. Poole, UK. De-ionized water was used.

2.4 METHODS

2.4.1 Preparation of acid and buffer solutions

Hydrochloric acid solution (pH 1.2 HCl) was prepared by diluting 100 ml 5 M HCl to 5 L with water. Phosphate buffer (0.05 M) with different pH values were prepared by mixing 50 ml of 0.2 M potassium dihydrogen orthophosphate with different amounts of 0.2 M sodium hydroxide, and then diluting to 200 ml with water. The quantities of 0.2 M sodium hydroxide were 3.72, 5.70, 8.60 and 23.65 ml for pH 5.8, 6.0, 6.2 and 6.8 buffer respectively.

2.4.2 Solubility of organic acids

The solubility of citric acid and succinic acid in different dissolution media (pH 1.2 HCl and pH 6.8 phosphate buffer, 37 °C) was determined by adding increasing amounts of organic acid to the media until no more acid could be dissolved.
The solubility of sorbic acid, benzoic acid, fumaric acid, and adipic acid was determined using UV spectrophotometry. An excess amount of organic acid was added to 30 ml pH 1.2 HCl and pH 6.8 phosphate buffer respectively. The mixture was equilibrated for 2 hours at 37 °C and the undissolved solid was removed by filtration. The saturated solution was diluted to an appropriate concentration and the UV absorbance was determined under the peak wavelength of individual acid. The calibration curves of the UV absorbance to the concentration of a number of organic acid solutions in pH 1.2 HCl and pH 6.8 phosphate buffer were measured. The solubility of organic acids in these two media was calculated using these calibration curves.

2.4.3 Preparation of polymeric films

2.4.3.1 Eudragit® L 100-55 films (organic)

Eudragit® L 100-55 films were prepared from organic (ethanolic) solutions. Three types of film were prepared: i) control film, ii) organic acid-containing film without TEC and iii) organic acid-containing film with TEC. TEC is the recommended plasticizer for Eudragit® L 100-55 and Eudragit® L 30 D-55 enteric coatings as it efficiently decreases Tg and increases the flexibility of the polymer film (Gutierrez-Rocca and McGinity, 1994; Felton et al., 1995). The recommended concentration of TEC for Eduragit® L 100-55 is 10%, based on the weight of the dry polymer. Therefore, 10% TEC-containing Eudragit® L 100-55 film was used as the control film. It is not feasible to prepare pure Eudragit® L 100-55 film, due to the brittleness of the film caused by the lack of plasticization.

Organic solutions for casting film were prepared as follows:
A 10% (w/v) ethanolic Eudragit® L 100-55 solution with or without organic acid was prepared by dissolving TEC and/or organic acid (% w/w, based on the dry
polymer) in 96% ethanol, and then stirring Eudragit® L 100-55 into the solution. The mixture was kept stirring for 1-2 hour until a clear solution was obtained.

Films (thickness 120-150 μm) were prepared by casting 10 ml above mentioned ethanolic solution onto Teflon dishes (round, r = 4.5 mm). Films were dried at room temperature for 12 hours, and then in an oven at 50 °C for 24 hours. Thickness of the film was measured at five different points. If the SD (standard deviation) of the five thickness measurements was greater than 10% of the mean thickness, the film was not included for further testing. The same measurement and standard for film thickness were used for the following study.

2.4.3.2 Eudragit® L 30 D-55 films (aqueous)

Eudragit® L 100-55 films were smooth with 10% TEC in the film; however, Eudragit® L 30 D-55 films cast from aqueous dispersion did not have a smooth surface when TEC concentration in the film was lower than 20%. This is attributable to the different film formation processes for organic solution and aqueous dispersion. The inter-particle forces exerted by the evaporation of water from aqueous dispersion during particle coalescence result in the uneven film formation. Higher amounts of plasticizer are required for aqueous dispersion than organic solution to weaken the polymer intermolecular attractions and increasing the polymer’s free volume, thus allowing the polymer molecules to move more freely to form a smooth film. Therefore, 20% TEC was included in all of the Eudragit® L 30 D-55 aqueous film formulations.

Partial neutralization of Eudragit® L 30 D-55 dispersion

Sorbic acid and fumaric acid were added into Eudragit® L 30 D-55 dispersion for casting aqueous films. During the film preparation, it was not possible to dissolve sorbic acid and fumaric acid in water to prepare films with acid concentrations
above 5%, due to the low water solubility of the acids. To dissolve these acids in water, 1 M NaOH were added into the solution. After adding the acid solution into Eudragit® L 30 D-55 dispersion, the pH value of the final dispersion was adjusted to 5.5 using 1 M NaOH. The normal pH value of Eudragit® L 30 D-55 dispersion is 3.0-3.3, slightly variable between different batches. For comparison, the pH of Eudragit® L 30 D-55 dispersion containing TEC but without organic acid was also adjusted to 5.5 using 1 M NaOH.

The acid value of Eudragit® L 30 D-55 is described that 300-330 mg KOH is consumed to completely neutralize the methacrylic acid groups of 1 g Eudragit® L 30 D-55 polymer (Technical bulletin, 2005, Degussa Röhm Pharma Polymers). For Eudragit® L 30 D-55 dispersion containing TEC but without organic acid, based on the amount of 1 M NaOH consumed to adjust the dispersion pH, the neutralization value of the methacrylic acid group of the polymer can be calculated. When adjusting the dispersion pH to 5.5, about 10% of the methacrylic acid group was neutralized. With the presence of organic acid, since the methacrylic acid in the polymer and the organic acid were neutralized simultaneously by the addition of 1 M NaOH, it is not possible to calculate the exact neutralization value of the polymer. However, at the dispersion pH of 5.5, both the Eudragit® L 30 D-55 polymer and the organic acid were partially neutralized by the addition of 1 M NaOH.

Eudragit® L 30 D-55 dispersion was also neutralized to pH 5.6 using 1 M NaOH in the presence of 10% adipic acid. It was observed that for this formulation, the dispersion changed to a clear solution with the complete dissolution of polymer particles immediately after the dispersion pH reached 5.6. Pure Eudragit® L 30 D-55 dispersion without the presence of adipic acid was compared by neutralizing to the same pH using 1 M NaOH. For pure Eudragit® L 30 D-55 dispersion to change to a clear solution, it took 16 hours under stirring after the dispersion pH reached 5.6, which is the pH value slightly higher than the dissolution pH threshold of the polymer (pH 5.5).
**Preparation of Eudragit® L 30 D-55 aqueous formulations:**

**TEC film:** A 10% (w/v) Eudragit® L 30 D-55 aqueous dispersion was prepared by dissolving TEC in water, and then stirring the TEC solution into Eudragit® L 30D-55 dispersion.

**TEC, pH 5.5 film:** A 10% (w/v) Eudragit® L 30 D-55 aqueous dispersion was prepared by dissolving TEC in water, and then stirring into Eudragit® L 30 D-55 dispersion. The pH of the dispersion was then adjusted to 5.5 using 1 M NaOH.

**Organic acid and TEC, pH 5.5 film:** An organic acid (sorbic acid/fumaric acid) solution was prepared by adding organic acid into water, and drop wise addition of 1 M NaOH until a clear solution was obtained. A 10% (w/v) Eudragit® L 30 D-55 aqueous dispersion was prepared by dissolving TEC into the above mentioned organic acid solution, and then stirring into Eudragit® L 30 D-55 dispersion. The pH of the dispersion was then adjusted to 5.5 using 1 M NaOH.

**Organic acid and TEC, pH 5.6 film:** Adipic acid was included in this formulation and the same method as preparing organic acid and TEC, pH 5.5 film was used, while, the pH of the dispersion was adjusted to 5.6 using 1 M NaOH.

Films (thickness 120-150 μm) were prepared by casting 10 ml the above mentioned Eudragit® L 30 D-55 dispersions or solutions onto Teflon dishes (round, r = 4.5 mm). Films were dried at room temperature until they could be removed from the Teflon dish, and then continued to dry in an oven at 50 °C for 24 hours.

**2.4.4 Acid/buffer uptake and weight loss testing of films**

Acid-resistance of the films was evaluated using *acid uptake* (the amount of acid medium absorbed by the film) and *weight loss* of the films in acid medium. The
degree of the film dissolution in acid medium could be illustrated by its weight loss. The acid uptake shows the extent of acid medium absorption in the film. High acid uptake of enteric films can compromise the acid-resistance of the film coating and endanger acid-labile drugs.

Film dissolution performance in buffer was demonstrated by its buffer uptake and weight loss. The higher the weight loss rate in buffer indicates the quicker the film dissolution. The speed and extent of the buffer uptake could also help to understand the dissolution behaviour of the film.

Dried films were cut to 1cm*1cm square sheets, weighed (the original weight - Wo) and put into perforated bags (2*2 cm²). Bags with the film samples were placed in 30 ml of test medium (pH 1.2 HCl or pH 5.8, 6.0, 6.2 and 6.8 phosphate buffer), and shaken horizontally at 37 °C, 60 rpm in a shaking water bath (SS30, Grant Instruments Ltd. Cambridge, UK). Film samples were removed from the medium at predetermined time intervals and carefully blotted to remove the water on the film surface and then weighed at wet stage (the weight of wet film at time t - Wt). The wet films were dried at 50°C to a constant weight and the dried films were weighed again (the weight of dried film – Wd). At each sample time point, individual film was used and single test was conducted.

The acid/buffer uptake and weight loss of the films were calculated from Equations 1 and 2.

\[
\% \text{ acid/buffer uptake} = \left[ \frac{(W_t - W_d)}{W_d} \right] \times 100 \quad \text{Eq. 1}
\]

\[
\% \text{ weight loss} = \left[ \frac{(W_o - W_d)}{W_o} \right] \times 100 \quad \text{Eq. 2}
\]
2.4.5 Differential scanning calorimetry

To understand the effect of plasticizer and organic acid on the dissolution of Eudragit® L 100-55 (organic) films, thermal properties of the films were determined using differential scanning calorimetry (DSC). For comparison, Eudragit® L 100-55 powder was also tested.

Eudragit® L 100-55 films were prepared using the methods described in Section 2.4.3.1. After drying, the films were stored in a desiccator over silica gel for 72 hours prior to analysis using DSC (Pyris 1, PerkinElmer Instruments, Bucks, UK). Approximately 10 mg of sample was weighed and sealed into an aluminum pan. The samples were heated at a rate of 200 °C/minute from -20 to 160 °C. High heating rate was applied to obtain a clear glass transition temperature ($T_g$) because of the high focus of the heating capacity. The $T_g$ values of the sample were reported as the half change in specific heat capacity of the transition.

To eliminate the influence of residual solvent, samples were heated twice, and the second heating results were used for data analysis. The test was performed in triplicate.

2.4.6 Determination of sodium concentration in the films

For organic acid-containing Eudragit® L 30 D-55 film, which was cast from dispersions with the pH value adjusted to 5.6 using 1 M NaOH, the concentrations of sodium in the film before and after testing in pH 1.2 HCl were determined. This test was carried out to provide information of ion exchange between the film and the acid medium. The determination of sodium concentration in the film was conducted by using scanning electron microscopy/energy dispersive X-ray spectroscopy (SEM/EDX).
2.4.6.1 Theory of SEM/EDX

Energy dispersive X-ray spectroscopy (EDX, also referred to as EDS) is a chemical microanalysis technique, which is performed in conjunction with scanning electron microscope (SEM). EDX allows the analysis of the molecular composition of a sample. It could be used to qualitatively and quantitatively analyze the elements present in a selected area of the SEM image.

During EDX analysis, the sample is bombarded by the electron beam of the SEM. Electrons of the atoms comprising the surface of the sample are ejected by this bombardment, resulting in an electron vacancy. The vacancy is eventually filled by an electron from a higher shell, and an X-ray is emitted to balance the energy difference between the two electrons.

The emitted X-ray from each element of the sample has a unique amount of energy. By measuring the amounts of energy present in the X-rays being released by a sample, EDX detector can identify the elements present in the sample. The output of an EDX analysis is an EDX spectrum (Figure 2.3). The spectrum displays peaks corresponding to the energy levels for which the most X-rays had been received. Each of the peaks represents a single element of the sample. The higher a peak for an element, the more concentrated the element is in the sample.
Not only can the concentration of an element in the sample be determined by EDX analysis, the distribution of the element on the sample surface can also be detected. This can be conducted by EDX mapping, which records the X-ray intensity of the element across the surface of the sample.

2.4.6.2 SEM/EDX testing

Organic acid-containing (pH 5.6) Eudragit® L 30 D-55 films were prepared using the methods described in section 2.4.3.2. The films were placed in pH 1.2 HCl at 37 °C for 2 hours and dried. The cross-sections of the film before and after acid treatment were examined by SEM using a JEOL JSM-840A Scanning Microscope. Sodium concentration at the SEM determined area of the cross-section of the film was determined using an EDX spectrooscope (model OXFORD INCA 200), equipped with a Liquid Nitrogen cooled X-ray detector (Si(Li) - silicon with lithium) having 10 mm² crystal area. The working distance for the EDX detector was 15 mm ± 1 and the electron energy (acceleration voltage) was 15 keV. All the samples for EDX testing were coated with carbon (~ 30 -40 nm).
2.5 RESULTS AND DISCUSSION

2.5.1 Solubility of organic acids

Although the solubility of organic acids in pH 1.2 HCl and pH 6.8 buffer has been reported in the literature, the values were obtained at room temperature (Peamchob et al., 2004). To better resemble in vivo conditions, these solubility values were determined in this study at 37 °C. Table 2.3 compares the solubility values of organic acids obtained in this study and the literature. Although the temperature used is higher than in the literature, the solubility data obtained in this study is in general lower. This is attributable to the different test methods used in the two studies. In the literature, the solubility of organic acids was determined using visual testing by continually adding acids to the medium until a saturated solution was achieved and solid could be seen, whereas UV spectrophotometry was applied in this study to determine the solubility of organic acids with low water solubility. In addition, the test buffer used in the two studies could be different (phosphate buffer were used in both studies; however, the type and concentration of the buffer used in the literature was not reported). The buffer capacity and ionic strength of the buffer solution can influence the solubility of ionizable acids (Nelson, 1958; Spitael and Kinget, 1977a; Shek, 1978; Kararli et al., 1995).

The result shows that at 37 °C, fumaric acid presents the biggest solubility difference between pH 1.2 HCl and pH 6.8 phosphate buffer, followed by sorbic acid, adipic acid and benzoic acid sequentially. Succinic acid and citric acid have high water solubility and very small or no solubility difference between pH 1.2 HCl and pH 6.8 phosphate buffer.
Table 2.3. Solubility of organic acids

<table>
<thead>
<tr>
<th>Name</th>
<th>Solubility (mg/ml)</th>
<th>Data obtained in this study (37 °C)</th>
<th>Literature (25 °C) (Yalkowsky and He, 2003; Peamchob et al., 2004)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.1N HCl pH 6.8</td>
<td>0.1N HCl pH 6.8 water</td>
<td></td>
</tr>
<tr>
<td>Sorbic acid</td>
<td>2.4</td>
<td>10.4</td>
<td>1-2 15-16 2.5</td>
</tr>
<tr>
<td>Benzoic acid</td>
<td>4.3</td>
<td>7.6</td>
<td>3-4 22-23 3.3</td>
</tr>
<tr>
<td>Fumaric acid</td>
<td>0.2</td>
<td>13</td>
<td>4-5 20-21 6.3</td>
</tr>
<tr>
<td>Adipic acid</td>
<td>16.2</td>
<td>45.1</td>
<td>24-25 48-49 0.32</td>
</tr>
<tr>
<td>Succinic acid</td>
<td>88-100</td>
<td>124-126</td>
<td>- - 70</td>
</tr>
<tr>
<td>Citric acid</td>
<td>&gt;1000</td>
<td>&gt;1000</td>
<td>&gt;1000 &gt;1000 380</td>
</tr>
</tbody>
</table>

2.5.2 The inclusion of organic acids in Eudragit® L 100-55 films

Two organic acids, sorbic acid and fumaric acid, with the biggest solubility differences in acid medium and buffer were included in Eudragit® L 100-55 film. The acid-resistance of the film and the film dissolution in buffer were tested as separate stage to differentiate the influence of acid and buffer medium on the dissolution performance of the film.

Acid-resistance of the films

Acid-resistance of the films was demonstrated using acid uptake and weight loss of the film in acid medium. Figure 2.4 shows the acid uptake and weight loss of 10% TEC, sorbic acid and fumaric acid-containing Eudragit® L 100-55 films in pH 1.2 HCl. Ten percent TEC-containing film had about 4% weight loss after treatment in pH 1.2 HCl for 2 hours. Since the polymer was not soluble at this pH value, the
weight loss is attributable to the leaching of the plasticizer TEC from the film. At room temperature, TEC was soluble in water at a concentration of 70 mg/ml (Gutierrez-Rocca and McGinity, 1994). The leaching of this water soluble plasticizer and other water soluble excipients from insoluble film coatings in dissolution medium has been well reported in the literature (Spitaël and Kinget, 1977b; Lecomte et al., 2004; Gruetzmann and Wagner, 2005; Bando and McGinity, 2006a; Bando and McGinity, 2006b).

\[(a)\]

\[\begin{align*}
\text{Acid uptake (\%)} \\
0 & \quad 20 & \quad 40 & \quad 60 & \quad 80 & \quad 100 & \quad 120 \\
0 & \quad 20 & \quad 40 & \quad 60 & \quad 80 & \quad 100 & \quad 120 \\
\end{align*}\]

\[\begin{align*}
\text{Time (min)} \\
0 & \quad 20 & \quad 40 & \quad 60 & \quad 80 & \quad 100 & \quad 120 \\
0 & \quad 20 & \quad 40 & \quad 60 & \quad 80 & \quad 100 & \quad 120 \\
\end{align*}\]

\[\begin{align*}
10\% \text{ TEC} \\
10\% \text{ Sorbic acid} \\
10\% \text{ Fumaric acid} \\
\end{align*}\]

\[(b)\]

\[\begin{align*}
\text{Weight loss (\%)} \\
0 & \quad 20 & \quad 40 & \quad 60 & \quad 80 & \quad 100 & \quad 120 \\
0 & \quad 20 & \quad 40 & \quad 60 & \quad 80 & \quad 100 & \quad 120 \\
\end{align*}\]

\[\begin{align*}
\text{Time (min)} \\
0 & \quad 20 & \quad 40 & \quad 60 & \quad 80 & \quad 100 & \quad 120 \\
0 & \quad 20 & \quad 40 & \quad 60 & \quad 80 & \quad 100 & \quad 120 \\
\end{align*}\]

\[\begin{align*}
10\% \text{ TEC} \\
10\% \text{ Sorbic acid} \\
10\% \text{ Fumaric acid} \\
\end{align*}\]

**Figure.** 2.4. Acid uptake (a) and weight loss (b) as functions of time for Eudragit® L 100-55 films with TEC or organic acids in pH 1.2 HCl.
Fumaric acid and sorbic acid-containing films exhibited the same weight loss values as TEC-containing film. Since the solubility of fumaric acid and sorbic acid are lower than TEC, the same extent of weight loss of the film is likely due to the lower compatibility of these acids with Eudragit® L 100-55 film compared to TEC. Figure 2.5 shows the scanning electron microscopy (SEM) images of 10% sorbic acid, fumaric acid and TEC-containing films. Pure Eudragit® L 100-55 film was clear but with large cracks due to the lack of plasticization. With 10% TEC, the film showed a clear and much smoother surface, indicating the good compatibility and plasticization effect of TEC to the film. However, with the addition of 10% of both sorbic acid and fumaric acid, the film appeared cloudy and large crystals could be seen on the surface, which indicates poor compatibility of the acids with the film.

![Scanning electron micrographs of the surfaces of Eudragit® L 100-55 films.](image)

**Figure 2.5.** Scanning electron micrographs of the surfaces of Eudragit® L 100-55 films.
Although TEC has higher water solubility than the acids, as a good plasticizer, TEC molecules are able to access the intra-polymer structure of Eudragit® L 100-55 and form hydrogen bonds with the polymer (Gutierrez-Rocca and McGinity, 1994), which contributed to the low weight loss of the film in acid medium.

Fumaric acid-containing film showed similar acid uptake as TEC-containing film, whereas, the acid uptake of the film containing sorbic acid was slightly higher. This is possibly due to the slightly higher solubility of sorbic acid in pH 1.2 HCl than fumaric acid. In general, the low acid uptake and weight loss of sorbic acid and fumaric acid-containing films indicate good acid-resistance of the films.

**Film dissolution in buffer**

The dissolution of 10% sorbic acid, fumaric acid and TEC-containing Eudragit® L 100-55 films was determined in pH 5.8, 6.2 and 6.8 phosphate buffer. Figure 2.6 shows the buffer uptake and weight loss of these films in pH 6.2 phosphate buffer. The complete film dissolution occurred at about 1, 2.5 and > 3 hours after exposure to buffer for TEC, sorbic acid and fumaric acid formulation respectively. In pH 5.8 phosphate buffer, all of these films dissolved very slowly, not more than 30% dissolved after 3 hours (data not shown). The films all dissolved rapidly in pH 6.8 phosphate buffer, almost completely dissolved within 20 minutes.

The film dissolution speed in pH 6.2 buffer is more beneficial for discriminating the performance of different film formulations compared to the pH 5.8 and 6.8 buffer. Therefore, it was applied for testing the dissolution of Eudragit® L 100-55 films in the following study.
As shown in Figure 2.6, organic acid-containing films presented slower buffer uptake and weight loss rate than TEC-containing film, indicating that including sorbic acid and fumaric acid in Eudragit® L 100-55 films could not accelerate the
film dissolution. Pearnchob et al. (2004) reported that the inclusion of 10% sorbic acid in shellac film can accelerate the film dissolution, with a decrease in the disintegration time of shellac-coated soft gelatin capsules in pH 6.8 phosphate buffer from about 60 minutes to 5-25 minutes. Since shellac is also an enteric polymer, the results from this study are different from the reported findings. The reasons of the different effects of adding organic acids in shellac film and Eudragit® L 100-55 film are discussed as follows.

Pearnchob et al. (2004) reported that sorbic acid acted as an effective plasticizer for shellac film, with even higher efficiency to decrease the Tg of shellac film than commonly used plasticizer TEC. Plasticization of polymeric films is normally necessary to obtain an effective film coating. The addition of plasticizer could reduce the minimum film-forming temperature and glass transition temperature (Tg) and increase the flexibility of the film. These effects are achieved by the plasticizer reducing the intermolecular forces along the polymer chains and increasing the free volume of the polymer (Banker, 1966; Lippold and Pages, 2001). For a plasticizer to be effective, the plasticizer must be able to diffuse and interact between the polymer chains. The affinity of plasticizers for the polymer could be characterized by its compatibility with the polymer which is reflected by the miscibility of these two components (Florence, 1984).

As shown by the SEM images, the compatibility of sorbic acid and fumaric acid with Eudragit® L 100-55 film was very poor. Ten percent sorbic acid and fumaric acid-containing films were cloudy and showed large crystals on the film surface, which indicates poor plasticization effects of the acids to the film. This is also confirmed by DSC results. The DSC thermogram of Eudragit® L 100-55 film with 10% TEC was shown in Figure 2.7. Table 2.4 provides the Tg values of Eudragit® L 100-55 powder and Eudragit® L 100-55 films with 10% TEC and organic acids.
Figure 2.7. DSC thermogram of Eudragit® L 100-55 film with 10% TEC.

Table 2.4. $T_g$ values as obtained by DSC of Eudragit® L 100-55 powder and films with TEC and organic acids (mean±SD)

<table>
<thead>
<tr>
<th>Formulation</th>
<th>$T_g$ (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eudragit® L 100-55 powder</td>
<td>131.97±1.84</td>
</tr>
<tr>
<td>Pure Eudragit® L 100-55 film</td>
<td>125.06±0.86</td>
</tr>
<tr>
<td>10% TEC-containing film</td>
<td>79.97±1.07</td>
</tr>
<tr>
<td>10% Sorbic acid-containing film</td>
<td>95.87±2.41</td>
</tr>
<tr>
<td>10% Fumaric acid-containing film</td>
<td>98.99±1.98</td>
</tr>
</tbody>
</table>

The DSC measurement shows that Eudragit® L 100-55 powder had higher $T_g$ value than its film. The lower $T_g$ value of polymer film compared to the powder has also
been observed by Fadda (2007) with Eudragit® S. This was associated to the solvent residue in the film which acted as a plasticizer for reducing the $T_g$.

Including 10% TEC in Eudragit® L 100-55 film reduced the $T_g$ of the film from about 125 °C to 80 °C. This demonstrates the good plasticization effect of TEC to Eudragit® L 100-55 film. However, the decrease in the $T_g$ value was smaller by the inclusion of sorbic acid and fumaric acid in the film compared to TEC, indicating the less plasticization effect of the organic acids to the film.

The hydration of polymeric films can be enhanced by increasing the mechanical flexibility of the film which is the result of plasticization effect (Narisawa et al., 1996). This can explain the acceleration effect of sorbic acid to the dissolution of shellac film due to the good plasticization effect. In addition, compared to Eudragit® L 100-55, shellac coating has slow dissolution rate in intestinal pH conditions, which can be attributed to its relatively high $pK_a$ of between 6.9 and 7.5 (Cole, 1995). Pearnchob et al. (2004) tested organic acid-containing shellac films in pH 6.8 phosphate buffer. The ionization and dissolution of sorbic acid at this buffer pH is possibly faster than shellac film due to its lower $pK_a$ value. However, the $pK_a$ of the methacrylic acid group of Eudragit® L 100-55 is 4.6, much lower than shellac, and thus the dissolution of Eudragit® L 100-55 in intestinal pH conditions is much faster. The ionization of sorbic acid and fumaric acid may not be faster than Eudragit® L 100-55 polymer, and therefore the addition of the acids was not able to accelerate the dissolution of the film.

Addition of TEC in organic acid-containing films

Based on above discussion, to achieve good film flexibility, it would be desirable to include TEC in organic acid-containing Eudragit® L 100-55 films. Acid uptake and weight loss of these organic acid containing films with 10% TEC in pH 1.2 HCl are shown in Figure. 2.8. Both the acid uptake and weight loss of 10% sorbic acid and
10% fumaric acid-containing films with TEC are very close to the film containing 10% TEC but without organic acid. These results indicate good acid-resistance of the films.

(a)

Figure 2.8. Acid uptake (a) and weight loss (b) as functions of time for Eudragit® L 100-55 films with TEC and organic acids in pH 1.2 HCl.
Figure 2.9 shows the dissolution behavior of these organic acid and TEC-containing films in pH 6.2 phosphate buffer. As expected, adding TEC into organic acid-containing film increased the rate of its buffer uptake and weight loss. For 10% fumaric acid-containing film, buffer uptake and weight loss was still slower than the film containing 10% TEC but without organic acid, indicating that adding fumaric acid into Eudragit® L 100-55 film did not increase but decreased its dissolution. This is probably due to the low water solubility of fumaric acid. Adding sorbic acid into the film obtained similar results as the TEC-containing film, and the buffer uptake and weight loss did not increase with increasing sorbic acid concentration from 10% to 20%.

These results demonstrated that the inclusion of low water soluble organic acids such as sorbic acid and fumaric acid into Eudragit® L 100-55 films was not able to accelerate the film dissolution in buffer. The effects of organic acids having higher water solubility than sorbic acid and fumaric acid, such as adipic acid, citric acid and succinic acid on the dissolution of Eudragit® L 100-55 films were then investigated. The acid uptake and weight loss of the films in pH 1.2 HCl were substantially increased due to the inclusion of these high water soluble acids (data not shown). This indicates the leaching of the acids from the film in acidic medium. In subsequent buffer, the film dissolution rate was not increased.

Properties of films obtained from organic solvent solution and aqueous dispersion can be different due to the different film formation processes (Lippold and Pages, 2001). These properties include physicochemical properties, acid-resistance and in vitro drug release (Chang, 1990; Lorck et al., 1997; Sutch et al., 2003; Ibekwe et al., 2006a). It is presumable that organic acids may have different effects on the dissolution properties of Eudragit® L 30 D-55 films (aqueous) compared to Eudragit® L 100-55 films (organic). Therefore, the inclusion of organic acids in Eudragit® L 30 D-55 films was investigated in the following sections of the study.
Figure 2.9. Buffer uptake (a) and weight loss (b) as functions of time for Eudragit® L 100-55 films with TEC and organic acid in pH 6.2 phosphate buffer.
2.5.3 The inclusion of organic acids in Eudragit® L 30 D-55 (aqueous) films

2.5.3.1 Organic acids with low water solubility

As described in Section 2.4.3.2, the pH of Eudragit® L 30 D-55 dispersions was adjusted to 5.5 using 1 M NaOH with or without the presence of sorbic/fumaric acid. Eudragit® L 30 D-55 in the resultant film cast from the above dispersions was partially neutralized.

Acid-resistance of partially neutralized Eudragit® L 30 D-55 films

Non-neutralized Eudragit® L 30 D-55 film containing 20% TEC (having a normal pH) and partially neutralized film with 20% TEC (having a pH of 5.5) presented the same acid uptake and weight loss in pH 1.2 HCl (Figure 2.10). This demonstrates that the partial neutralization of Eudragit® L 30 D-55 aqueous dispersion which contains TEC but without organic acid has no influence on the film performance in acid medium.

The weight loss of Eudragit® L 30 D-55 films containing sorbic acid/fumaric acid and neutralized to pH 5.5 increased slightly in pH 1.2 HCl compared to TEC-containing films. However, the acid uptake of the organic acid-containing partially neutralized films was higher than TEC-containing film (Figure 2.10). Sorbic acid-containing film showed higher acid uptake than fumaric acid-containing film, which is likely due to the higher water solubility of sorbic acid. The low weight loss of the organic acid-containing partially neutralized films indicates that Eudragit® L 30 D-55 polymer and the additives remained in the film in acid medium. However, the increased acid uptake of the film can compromise the acid-resistance, and therefore cause the degradation of acid-liable drugs and/or the premature drug release in the stomach.
Figure 2.10. Acid uptake (a) and weight loss (b) as functions of time for Eudragit® L 30 D-55 films with TEC and organic acids in pH 1.2 HCl.
Film dissolution in buffer

To optimize the buffer pH for testing Eudragit® L 30 D-55 films, buffer uptake and weight loss of 20% TEC-containing Eudragit® L 30 D-55 film were tested in pH 6.0 and pH 6.2 phosphate buffer (data not shown). pH 6.0 phosphate buffer was shown to be more advantageous for discriminating the performance of different aqueous film formulations due to the slower film dissolution.

Partially neutralizing the film containing TEC but without organic acid to pH 5.5, the rate of its buffer uptake and weight loss did not change (Figure 2.11), which further confirms that the partial neutralization of Eudragit® L 30 D-55 dispersion to this pH value had no influence on film dissolution properties. However, with the presence of 5% sorbic acid or fumaric acid and neutralizing to pH 5.5, the dissolution rate of the film in pH 6.0 phosphate buffer was increased substantially compared to the film containing TEC but without organic acid (Figure 2.11). The weight loss for sorbic acid, fumaric acid and TEC-containing films was 74, 66 and 22% respectively after 20 minutes in buffer. The buffer uptake of sorbic acid/fumaric acid-containing films was very fast and the extension of buffer content in the film reached very high level. Its maximum buffer content achieved within 15 minutes and the film became transparent. After 20 minutes exposure to buffer, most of the film has dissolved.

The dissolution rate of partially neutralized films with sorbic acid was faster than with fumaric acid. To evaluate the influence of sorbic acid concentration on film dissolution, films containing 2, 5 and 10% sorbic acid and all neutralized to pH 5.5 were tested in pH 6.0 phosphate buffer (data not shown). The rates of buffer uptake and weight loss of the films with different sorbic acid concentrations were in the order of: 5% > 10% > 2%.
Figure 2.11. Buffer uptake (a) and weight loss (b) as functions of time for Eudragit® L 30 D-55 films with TEC and organic acid in pH 6.0 phosphate buffer.

It has been established from the above results that including sorbic acid and fumaric acid in partially neutralized Eudragit® L 30 D-55 films can significantly accelerate its dissolution in buffer. In addition, 5% sorbic acid and neutralizing the dispersion pH to 5.5 provided the fastest film dissolution. It was then of interest to investigate
the effect of organic acids with higher water solubility and higher neutralization value of the dispersion on the film dissolution.

2.5.3.2 Organic acids with high water solubility

Adipic acid which has higher water solubility than sorbic/fumaric acid was included into Eudragit® L 30 D-55 dispersion and the pH of the dispersion was adjusted to pH 5.6 using 1 M NaOH. The dispersion was turned to a clear solution at this pH value with the presence of adipic acid.

Directly testing the film in buffer

The film cast from Eudragit® L 30 D-55 pH 5.6 solution in the presence of 10% adipic acid was tested in pH 6.0 phosphate buffer. The film dissolved so fast that it was not possible to remove it from the buffer medium. The film became transparent after 5 minutes and almost completely dissolved after 10 minutes exposure to buffer.

Acid resistance of the film

The adipic acid-containing pH 5.6 film was tested in pH 1.2 HCl, and the acid uptake of the film was much higher than TEC-containing non-neutralized film (218% and 37% respectively, Figure 2.12). In addition, the weight loss of this film was also higher than TEC-containing film, 13% and 8% for adipic acid and TEC-containing film respectively (Figure 2.12). These results indicate that the acid-resistance of the adipic acid-containing pH 5.6 film was poor due to absorbing high amount of acid medium. Also, adipic acid could leach out from this partially neutralized film in acid medium, due to its high hydrophilicity and permeability.
Figure 2.12. Acid uptake (a) and weight loss (b) as functions of time for Eudragit® L 30 D-55 films with TEC and adipic acid in pH 1.2 HCl.

Film dissolution in buffer after acid treatment

Although the adipic acid-containing partially neutralized film dissolved very fast when directly testing in pH 6.0 phosphate buffer, a large amount of acid medium was absorbed by the film in pH 1.2 HCl. It was therefore of concernment to test the
film dissolution properties in buffer after 2 hours acid exposure. Figure 2.13 demonstrated that after treatment in pH 1.2 HCl for 2 hours, in subsequent pH 6.0 buffer, the rate of weight loss and buffer uptake of adipic acid-containing partially neutralized film was not faster than the TEC-containing non-neutralized film.

(a)

![Graph](image)

(b)

![Graph](image)

Figure 2.13. Buffer uptake (a) and weight loss (b) as functions of time for Eudragit® L 30 D-55 films with adipic acid in subsequent pH 6.0 phosphate buffer after in pH 1.2 HCl for 2 hours.
**Ion exchange in acid medium**

When neutralizing Eudragit® L 30 D-55 dispersion to pH 5.6 in the presence of adipic acid, the aqueous dispersion changed to a solution. In this aqueous solution, the water insoluble Eudragit® L 30 D-55 polymer became water soluble due to the partial neutralization and ionization of the methacrylic acid groups of the polymer. It is not difficult to understand that films cast from this aqueous solution dissolved very fast when directly testing in buffer. However, after exposure to acid medium for 2 hours, the ionized methacrylic acid groups of the polymer which was in the form of conjugate base as the sodium salt was converted back to the free acid, due to the high acidity of hydrochloric acid (Equations 3 and 4).

\[
\text{R–} \overset{\text{C}}{\overset{\text{O}}{\overset{\text{O}}{\overset{\text{H}}{\overset{\text{–}}{\overset{\text{NaOH}}{\longrightarrow}}}}} \overset{\text{Na^+}}{\overset{\text{H^+}}{\overset{\text{H_2O}}{\longrightarrow}}} \text{R–} \overset{\text{C}}{\overset{\text{O}}{\overset{\text{O}}{\overset{\text{H}}{\overset{\text{–}}{\overset{\text{Na^+}}{\longrightarrow}}}}} \overset{\text{Na^+}}{\overset{\text{H_2O}}{\longrightarrow}}} \text{Eq. 3}
\]

\[
\text{R–} \overset{\text{C}}{\overset{\text{O}}{\overset{\text{O}}{\overset{\text{H}}{\overset{\text{–}}{\overset{\text{Na^+}}{\longrightarrow}}}}} \overset{\text{Na^+}}{\overset{\text{H^+}}{\overset{\text{HCl}}{\longrightarrow}}} \overset{\text{NaCl}}{\overset{\text{H_2O}}{\longrightarrow}}} \text{Eq. 4}
\]

This ion exchange in acid medium was confirmed using SEM/EDX testing. Sodium concentration in Eudragit® L 30 D-55 films partially neutralized to pH 5.6 in the presence of 10% sorbic acid and adipic acid were determined before and after 2 hours acid exposure (Table 2.5). In the original films, there was 7-8% sodium due to the addition of 1M NaOH. However, after 2 hours acid treatment, only 0.5-0.7% sodium remained in the film. This illustrated that most of the sodium salts of the polymer were converted back to the free acid form. The loss of ionization properties of the polymer in acid medium can then explain its slow dissolution rate in subsequent buffer. It was also implicated that to maintain the fast dissolution
properties of the film in buffer, protection of the film in acid medium would be necessary.

Table 2.5. Sodium concentration in partially neutralized Eudragit\textsuperscript{R} L 30 D-55 films before and after acid treatment

<table>
<thead>
<tr>
<th>Film formulation</th>
<th>Sodium concentration (%) mass</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before acid treatment</td>
</tr>
<tr>
<td>10% Sorbic acid, pH 5.6</td>
<td>7.0</td>
</tr>
<tr>
<td>10% Adipic acid, pH 5.6</td>
<td>7.8</td>
</tr>
</tbody>
</table>

The concept of ion exchange of partially neutralized enteric polymers in acidic medium has been investigated to develop aqueous solution-based enteric coating systems for cellulose ester derivatives (Chang, 1990; O'Connor and Berryman, 1992; Heinamaki et al., 1994a; Heinamaki et al., 1994b; Bechard et al., 1995). The technique was used to replace the use of organic solvent and was achieved by neutralizing the free acid groups of the polymer with ammonium hydroxide. When the coated product is exposed to acidic medium, the polymer salt is transformed into the acid form and the enteric property is achieved. The gastric-resistance, mechanical properties and permeability of enteric coatings obtained from these aqueous ammonium solutions were extensively investigated (Chang, 1990; O'Connor and Berryman, 1992; Heinamaki et al., 1994a; Heinamaki et al., 1994b; Bechard et al., 1995).

Gastric-resistance can be achieved from these coatings, but their acid permeability was reported higher than the coating obtained from organic solvent solutions, which
makes them unsuitable for acid-labile drugs (Chang, 1990; O'Connor and Berryman, 1992; Heinamaki et al., 1994a; Bechard et al., 1995). The films swell in acidic medium and the acid uptake is high, which is in agreement with the findings in this study with partially neutralized Eudragit® L 30 D-55 films. However, investigations of these neutralized aqueous coating systems were intensively focused on the gastric-resistant properties; the drug release and film dissolution properties after the acid treatment were rarely compared with organic coatings. In the present study, the dissolution of partially neutralized Eudragit® L 30 D-55 films after the acid treatment was compared with non-neutralized film and showed no difference. This indicates that the complete transformation of the polymer salt to acid form in acid medium eliminated the influence of the partial neutralization on the film dissolution in subsequent buffer.

In summary, organic acid-containing partially neutralized Eudragit® L 30 D-55 film exhibited very fast dissolution when directly testing in buffer. However, the film dissolution became slow after acid treatment due to the ion exchange in acid medium. To maintain the fast film dissolution properties in buffer, a protection of these films in acid medium would be beneficial. This is exploited in Chapter 3.
SECTION 2: THE USE OF pH-SENSITIVE POLYMERS IN EUDRAGIT® L 30 D-55 FILMS

2.6 INTRODUCTION

Low molecular weight components, such as organic acids, leached out from Eudragit® L 100-55 and Eudragit® L 30 D-55 films during acid treatment, and thus were not able to assist the film dissolution in subsequent buffer. It is conceivable that components with high molecular weight, such as polymers, are more likely to remain in the film. Polymers such as pectin, alginates (including alginic acid and sodium alginate) and xanthan gum also have pH-sensitive dissolution properties due to the presence of anionic groups in their structures, which are un-ionizable below and ionizable above the polymer’s pKa. However, different from low molecular weight organic acids, the pH-sensitive dissolution properties of these polymers are not only reflected by the different water solubility at low and high pH conditions. Due to the inter-chain entanglements in polymeric structure, in high pH medium, the ionized carboxylic groups of the polymer repel each other, and a remarkable amount of water can be absorbed into the polymer chains. This water uptake can contribute to a high swelling ratio of the polymer.

The pH-sensitive swelling properties of these polymers are of particular interest for modifying enteric coatings. On incorporation of these pH-sensitive polymers into enteric coatings, their high swelling ability could substantially enhance the water absorption by the enteric film at high pH conditions, thus assisting its dissolution. However, the acid-resistance properties of the enteric coating could be maintained due to the low swelling rate of these pH-sensitive polymers in acid medium. Pectin, alginic acid, sodium alginate and xanthan gum are anionic polymers obtained from natural sources, thus giving them a safety benefit. The chemical structures,
dissolution and swelling properties of these polymers are discussed in the following section.

2.6.1 Properties of pH-sensitive polymers

2.6.1.1 Pectin

Pectin is an anionic polysaccharide, primarily containing large amounts of poly(D-galacturonic acid) bonded via α-1, 4-glycosidic linkage (Figure 2.14).

![Chemical structure of pectin (Ralet et al., 2002).](image)

The gelling ability and solubility of pectin strongly depends on the pH of the surrounding media. At dissolution media of low pH (below 3.5, pKₐ of galacturonic acid) (Ralet et al., 2002), the ionization of the carboxylate groups of pectin is repressed. Pectin molecules no longer repel each other over their entire chain length, and thus can associate over a portion of their chains to form acid-pectin gels. For acid-induced pectin gels, the hydration of pectin is reduced and there is less water incorporated into interchain entanglements. However, once the solution pH is raised the polycarboxylate groups are ionized. Pectin gel thus has a remarkable water absorbing capacity ranging from 50 to 160 times the weight of the dry gel (Liu et al., 2003).
2.6.1.2 Alginates

Alginic acid, a hydrophilic and colloidal polysaccharide obtained from marine algae, is a linear copolymer consisting of $\beta$-(1→4)-D-mannuronic acid (M) and $\alpha$-(1→4)-L-guluronic acid (G) residues, arranged in homopolymeric blocks of each type (MM,GG) and in heteropolymeric blocks (MG) (Figure 2.15).

![Figure 2.15. Structural characteristics of alginates: (a) alginate monomers, (b) chain conformation, (c) block distribution (Draget et al., 2002).](image)

Alginic acid forms soluble salts with monovalent metal ions such as sodium whereas it easily gels in the presence of divalent cations such as calcium. Sodium alginate is soluble at near neutral aqueous medium; it does not swell at pH 1.2, however swells and erodes rapidly at pH 6.8 (Efentakis et al., 2000).

2.6.1.3 Xanthan gum

Xanthan gum is a heteropolysaccharide with high molecular weight produced by fermentation with the gram-negative bacterium *Xanthomonas campestris*. The
dominant sugar units present in xanthan are D-glucose and D-mannose, along with D-glucuronic acid (Figure 2.16).

\[ \text{Chemical structure of xanthan (Born et al., 2002).} \]

The anionic character of this polymer is due to the presence of both glucuronic acid and pyruvic acid groups in the side chain. Being an anionic polymer with a pK\text{a} of 3.1, xanthan gum presents a high pH-dependent swelling behaviour with a higher swelling degree in high pH solution than in low pH solution. Xanthan gum shows a strong degree of water uptake when in contact with aqueous medium (= 1300% weight increase after 8 hours) (Munday and Cox, 2000). Talukdar and Kinget (1995) investigated the swelling behaviour of xanthan gum matrix. They found it to hydrate quickly and no lag time of swelling could be detected. The swelling rate in 0.1 M HCl was significantly (p < 0.05) lower than in neutral or alkaline solutions.
2.6.2 The use of polymer blends in film coatings

Polymer blends have been investigated and applied in film coatings for different purposes. A blend of two or more different polymers can overcome the restrictions of the physicochemical properties of single polymer and achieve desired drug release profiles. A typical type of polymer blend in pharmaceutical coating is the addition of pore forming polymers, usually hydrophilic polymers such as hypromellose and hydroxypropyl cellulose, to ethylcellulose films in order to alter the drug release rates from sustained-release dosage forms (Gilligan and Li Wan Po, 1991; Umprayn et al., 1999). Pore forming agents were also used to modify drug release from water insoluble polymer Eudragit® RS coated sustained-release dosage forms (Zheng et al., 2005).

The use of polymer blends for colonic drug delivery has also been well documented in the literature. One approach for colonic drug delivery is to utilize polymer coatings which are susceptible to colon specific bacterial enzyme degradation. Natural polysaccharides such as pectin and amylose have been investigated for this purpose. However, these natural polymers commonly encounter problems related to high solubility or swelling in the upper small intestine due to their high hydrophilic nature. This problem can be solved by mixing them with water insoluble polymers such as ethylcellulose (Milojevic et al., 1996a; Milojevic et al., 1996b; Macleod et al., 1997; Leong et al., 2002).

Eudragit® polymers are also widely involved in polymer blends. The mixture of enteric polymer Eudragit® L 100 and the gastrointestinal (GI) tract -insoluble polymer, ethylcellulose, could prevent drug release in the stomach and provide a large range of drug release profiles by varying the enteric: GI-insoluble polymer blend ratio (Lecomte et al., 2003; Lecomte et al., 2004).
Various combinations of two Eudragit® polymers in film coatings have also been investigated. The mixture of two methacrylic acid copolymers having different dissolution pH, such as Eudragit® S 100/ Eudragit® L 100 and Eudragit® S 100/ Eudragit® L 100-55, can manipulate the drug release profiles within the pH range of 5.5 to 7.0 by changing the polymer ratios (Khan et al., 1999; Bando and McGinity, 2006a; Bando and McGinity, 2006b). For these coating systems, the active substances in the coated dosage forms could be theoretically delivered to any desirable region of the GI tract. Two pH-independent water insoluble but swellable Eudragit® polymers, Eudragit® RL (high permeable) and Eudragit® RS (low permeable), were also combined together for film coating to control the drug release rate from coated dosage forms (Amighi and Moes, 1995). A new trend of polymer combination is the formation of interpolyelectrolyte complexes by the reactions between oppositely charged polyions. The potential of forming interpolyelectrolyte complexes of Eudragit® E, a polycation, with polyanions such as Eudragit® L 100 and sodium alginate was confirmed in the literature and this interpolymer complex is of interest in sustained drug delivery systems (Moustafine et al., 2005a; Moustafine et al., 2005b; Moustafine et al., 2006).

Qussi and Suess (2005) reported the incorporation of different water soluble polymers in enteric polymer shellac coatings. Different amounts of polyvinyl alcohol, hypromellose, and carbomer 940 were included in shellac coating, and drug release from the coating in purified water was increased by the inclusion of these water soluble polymers. The mechanism of increasing drug release was shown to be either pore forming, cracks in the film or swelling on inclusion of hypromellose, polyvinyl alcohol or carbomer respectively. However, since shellac is water insoluble, but ionizable and soluble in small intestinal fluids, testing drug release from shellac coatings in water is not realistic. Drug release from these coating systems in pH 7.4 phosphate buffer was also determined; however, no significant improvement was shown by the inclusion of these water soluble polymers.
The aim of this section of the study was to investigate the effect of including pH-sensitive polymers in Eudragit® L 30 D-55 films on its dissolution properties. Pectin, alginic acid, sodium alginate and xanthan gum were used for the study. Since these pH-sensitive polymers are hydrophilic polymers, they are soluble or dispersible in water and most of them are practically insoluble in organic solvents; therefore in this stage of the study they were only incorporated into Eudragit® L 30 D-55 aqueous films. Dissolution properties of pure pH-sensitive polymer films and Eudragit® L 30 D-55 films containing different concentrations of these naturally-derived polymers were determined in acid medium and buffer solution.

2.7 MATERIALS

Eudragit® L 30D-55 was donated by Röhm GmbH, Darmstadt, Germany. Triethyl citrate (TEC) was purchased from Lancaster Synthesis, Lancashire, UK. Pectin (from apple), xanthan gum, alginic acid (from brown algae) and sodium alginate (from brown algae) were purchased from Sigma, St. Louis, MO, USA. All other reagents were of analytical grade. De-ionized water was used.

2.8 METHODS

2.8.1 Preparation of polymeric films

2.8.1.1 Preparation of pure pH-sensitive polymer films

Pure pectin, alginic acid, sodium alginate and xanthan films were prepared using aqueous solution or dispersion of the polymer. Preparation of the solutions and dispersions is described as follows:
**Pectin:** 2% pectin solution was prepared by slowly and steadily adding pectin to water and continuing to stir at room temperature until complete dissolution occurred.

**Alginic acid:** 10% alginic acid dispersion was prepared by slowly and steadily adding alginic acid to water, and continuing to stir at room temperature for 3-4 hours.

**Sodium alginate:** 2% sodium alginate solution was prepared by slowly and steadily adding sodium alginate to water at 40-50 °C, and continuing to stir at the same temperature until complete dissolution occurred.

**Xanthan gum:** 1% xanthan gum solution was prepared by slowly and steadily adding xanthan gum to water, and continuing to stir at room temperature until complete dissolution occurred.

Films (thickness 120-150 μm) were prepared by casting above mentioned solutions or dispersions onto Teflon dishes (round, r = 4.5 mm). Films were dried at room temperature until they could be removed from the Teflon dish, and then continued to dry in an oven at 50 °C for 24 hours.

It was not possible to prepare xanthan gum solution with a concentration higher than 1%, due to its high viscosity. The film thickness obtained from 1% xanthan solution was not sufficient for dissolution testing. Therefore, the dissolution of pure xanthan gum film was not determined.

### 2.8.1.2 Preparation of pH-sensitive polymer-containing Eudragit® L 30 D-55 films

Eudragit® L 30 D-55 films with and without pH-sensitive polymers were prepared using aqueous dispersions. Formulations for casting aqueous films were prepared using the following methods:
**TEC film:** A 10% (w/v) Eudragit® L 30 D-55 aqueous dispersion was prepared by dissolving TEC in water and then stirring the TEC solution into Eudragit® L 30 D-55 dispersion.

**pH-sensitive polymer-containing films:**

0.5% xanthan, 1% pectin, 2% sodium alginate and 10% alginic acid solutions or dispersion (alginic acid) were prepared by dissolving or dispersing the polymer in water. TEC was dissolved into Eudragit® L 30 D-55 dispersion by stirring for 90 minutes. The above pH-sensitive polymer solutions or dispersion were slowly poured into Eudragit® L 30 D-55 aqueous dispersion under stirring and continued to stir for 3-4 hours. Water was added to the final dispersion to adjust the solid content to 10%.

Films (thickness 120-150 µm) were prepared by casting 10 ml above mentioned Eudragit® L 30 D-55 dispersions onto Teflon dishes (round, r = 4.5 mm). Films were dried at room temperature until they could be removed from the Teflon dish, and then continued to dry in an oven at 50 °C for 24 hours.

**2.8.2 Acid/buffer uptake and weight loss testing of films**

Acid/buffer uptake and weight loss of the films were determined using the method described in Section 2.4.4.

**2.8.3 Determination of sodium concentration in the films**

Pure sodium alginate and Eudragit® L 30 D-55 films containing 10%, 20% and 50% sodium alginate were prepared using the methods described in Section 2.8.1. The films were placed in pH 1.2 HCl at 37 °C for 2 hours and dried. The cross-sections of the films were examined by scanning electron microscopy (SEM) using a JEOL JSM-840A Scanning Microscope. Sodium concentration at the SEM determined
area of the cross-section of the film was determined using energy dispersive X-ray spectroscopy (EDX) (model OXFORD INCA 200), equipped with a Liquid Nitrogen cooled X-ray detector (Si(Li) - silicon with lithium) having 10 mm² crystal area. The working distance for the EDX detector was 15 mm ± 1 and the electron energy (acceleration voltage) was 15 keV. All the samples for EDX testing were coated with carbon (~ 30 -40 nm). An EDX mapping was carried out to determine the sodium and carbon distribution in 50% sodium alginate-containing Eudragit® L 30 D-55 film by dividing the SEM picture of the cross-section of the films up into 512 x 384 points. Complete EDX spectra were produced (multiple and average) in every point and a spatial distribution of single element were extracted (using the INCA software).

2.9 RESULTS AND DISCUSSION

2.9.1 Dissolution properties of pure pH-sensitive polymer films

Films cast from pure pectin, alginic acid and sodium alginate aqueous solutions were tested in pH 1.2 HCl and subsequent pH 5.8 phosphate buffer. The dissolution properties of the films in terms of the acid/buffer uptake and weight loss were determined. Phosphate buffer with pH value of 5.8 was used to better discriminate the dissolution performance of different film formulations due to the fast dissolution of pH-sensitive polymer films. Xanthan gum formed very viscous aqueous solution at very low concentration (1%); therefore it was not possible to obtain pure xanthan film with suitable thickness for dissolution testing. Pure pectin film dissolved rapidly in pH 1.2 HCl. The film swelled to a large extent and lost its original shape after 30 minutes exposure to the acid medium and completely dissolved in acid after 60 minutes. The dissolution of pectin film in pH 1.2 HCl is attributable to the high water solubility of pectin. Since the pectin film dissolved in pH 1.2 HCl, the subsequent buffer testing was not carried out.
Although pure sodium alginate and alginic acid films swelled in pH 1.2 HCl and had higher acid uptake than Eudragit® L 30 D-55 film, the weight loss of the films remained low, similar to Eudragit® L 30 D-55 film (Figure 2.17). Alginic acid is insoluble in acid and sodium alginate is practically insoluble in aqueous acidic solution in which the pH is less than 3. These solubility properties contribute to the low dissolution level of the films in pH 1.2 HCl.

Compared to Eudragit® L 30 D-55 film, sodium alginate film dissolved much faster in pH 5.8 phosphate buffer following exposure to pH 1.2 HCl for 2 hours. Upon exposure to buffer, the film absorbed the buffer medium rapidly and swelled. The complete film dissolution occurred after 60 minutes (Figure 2.18). Alginic acid films dissolved slower in buffer than sodium alginate film after 2 hours acid treatment, however faster than Eudragit® L 30 D-55 film (Figure 2.18). After 120 minutes in buffer, alginic acid film completely dissolved. It is speculated that the low solubility of sodium alginate in pH 1.2 HCl and the fast buffer uptake and dissolution of its corresponding film in buffer could assist the dissolution of Eudragit® L 30 D-55 film.
Figure 2.17. Acid uptake (a) and weight loss (b) of pure alginates films and Eudragit® L 30 D-55 film in pH 1.2 HCl
Figure 2.18. Buffer uptake (a) and weight loss (b) of pure alginates films and Eudragit® L 30 D-55 film in subsequent pH 5.8 phosphate buffer after 2 hours in pH 1.2 HCl.
2.9.2 The inclusion of pH-sensitive polymers in Eudragit® L 30 D-55 films

2.9.2.1 Pectin and xanthan gum

Figure 2.19 shows that including 10% pectin in 20% TEC-containing Eudragit® L 30 D-55 film increased its acid uptake and weight loss in pH 1.2 HCl. After 2 hours of acid exposure, the weight loss of the film containing 10% pectin, 20% TEC was 17% higher than the film containing 20% TEC but without pectin. In addition, the acid uptake of the film with pectin was 3 times higher than the film without pectin. High weight loss of pectin-containing film indicates that pectin leached out from the film in pH 1.2 HCl. In addition, the swelling ratio of the film increased due to the inclusion of pectin which was reflected by the high acid uptake. The high swelling level of the film could also cause more TEC to leach out from the polymeric structure of the film.

After including pectin, 20% TEC plasticized Eudragit® L 30 D-55 film became brittle and developed cracks on the surface, therefore 40% TEC was used to make the film more flexible. Figure 2.19 shows that when increasing the TEC concentration in the film from 20% to 40%, the increase in the weight loss and acid uptake of the film was smaller compared to introducing 10% pectin in the film. This further confirmed that the high water solubility and hydrophilicity of pectin induced a higher level of swelling and dissolution of Eudragit® L 30 D-55 film in acid medium than TEC-containing film.
In subsequent pH 5.8 phosphate buffer after testing in pH 1.2 HCl for 2 hours, the dissolution of pectin-containing films was not faster than the TEC-containing film (Figure 2.20). This is attributed to the leaching of pectin from the film in pH 1.2 HCl, and thus no assistance in the film dissolution in buffer.
Figure 2.20. Buffer uptake (a) and weight loss (b) of Eudragit® L 30 D-55 film with different concentrations of pectin and TEC in subsequent pH 5.8 phosphate buffer after 2 hours in pH 1.2 HCl.

Xanthan gum was also included in Eudragit® L 30 D-55 film; however, xanthan with a concentration higher than 5% made Eudragit® L 30 D-55 dispersion too viscous for film casting. Therefore not more than 5% xanthan gum was included in the film. The dissolution properties of 5% xanthan-containing Eudragit® L 30 D-55 film were
similar to that of the pectin-containing films. The acid uptake and weight loss of the film were increased in pH 1.2 HCl after incorporating 5% xanthan in the film, indicating the high swelling rate of the film and the leaching of xanthan from it (data not shown). This is also attributable to the high water solubility of xanthan. In subsequent buffer testing, xanthan-containing films did not dissolve faster than the TEC-containing film.

The results with pectin and xanthan gum were different from the assumption that unlike low molecular weight components, high molecular weight polymers would remain in the film when testing in acid medium. In fact, these high molecular weight polymers also leached out from Eudragit® L 30 D-55 films. This can be attributed to the high water solubility and hydrophilicity of the polymers. In addition, the film formation processes from aqueous polymer dispersion could also provide an explanation for this leaching of the polymer.

The film formation process of pectin-containing Eudragit® L 30 D-55 dispersion is demonstrated in Figure 2.21. In the mixture of pectin aqueous solution and Eudragit® L 30 D-55 dispersion, pectin was in the form of polymer molecules, whereas, Eudragit® L 30 D-55 was in the form of polymer particles. After water evaporation, Eudragit® L 30 D-55 particles came into contact with one another, and the polymer chains of pectin distributed between Eudragit® L 30 D-55 particles. With further evaporation of water, the deformation and coalescence of Eudragit® L 30 D-55 particles took place by the driving forces exerted during the loss of water. However, the pectin chains between the particles hindered the coalescence process and resulted in the formation of less continuous film than the pure Eudragit® L 30 D-55 film. When testing this pectin-containing Eudragit® L 30 D-55 film in acid medium, the hydrophilicity of pectin induced swelling of the film, which in turn caused pectin molecules located between Eudragit® L 30 D-55 particles to leach out from the film.
Pectin molecules and Eudragit® L 30 D-55 particles in the dispersion

10% alginic acid was also included into Eudragit® L 30 D-55 film; different from pectin and xanthan-containing films, the inclusion of alginic acid did not increase the acid uptake and weight loss of the film in pH 1.2 HCl (data not shown). This indicates that alginic acid remained in the film and did not increase the swelling of the film in acid medium. This can be explained by the relatively low dissolution and water absorption value of pure alginic acid film in acid medium compared to pure pectin film. However, the presence of alginic acid in the film did not assist in film dissolution in the subsequent pH 5.8 buffer (data not shown). This can be attributed to the slow dissolution rate of alginic acid in buffer.

2.9.2.2 Sodium alginate

On inclusion of 5%, 10% and 20% sodium alginate into Eudragit® L 30 D-55 film, the acid uptake of the film increased very slightly following exposure to pH 1.2 HCl for 2 hours compared to the TEC-containing film (Figure 2.22). The weight loss of

Figure 2.21. Film formation process from pectin-containing Eudragit® L 30 D-55 dispersion
sodium alginate-containing films was higher than TEC-containing film especially with 5% and 10% sodium alginate. An increasing in the concentration of sodium alginate in the film from 10% to 20% was not accompanied by an increase in the film weight loss; this indicates that most of the sodium alginate remained in the film after 2 hours acid treatment.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure22a.png}
\caption{Acid uptake (a) and weight loss (b) of Eudragit® L 30 D-55 film with sodium alginate in pH 1.2 HCl}
\end{figure}
On exposure to pH 5.8 buffer post 2 hours pH 1.2 HCl, the dissolution of sodium alginate-containing Eudragit® L 30 D-55 films was not faster than the TEC-containing film (Figure 2.23). This behaviour is unexpected considering the dissolution properties of the pure sodium alginate film.

\[(a)\]

\[\text{Buffer uptake (\%) vs. Time (mins)}\]

\[(b)\]

\[\text{Weight loss (\%) vs. Time (mins)}\]

\textbf{Figure 2.23.} Buffer uptake (a) and weight loss (b) of Eudragit® L 30 D-55 film with sodium alginate in subsequent pH 5.8 phosphate buffer after 2 hours in pH 1.2 HCl.
The reason for this lack of acceleration of sodium alginate to the dissolution of Eudragit® L 30 D-55 films is not exactly known, however, it is speculated that the leaching of sodium ions from the film may be involved. Sodium alginate is the sodium salt of alginic acid and pre-exposing Eudragit® L 30 D-55 films with sodium alginate to pH 1.2 HCl may rise to sodium ions leaching out from the film due to ion exchange in acid. Thus the subsequent exposure to buffer does not accelerate the film dissolution.

To test this hypothesis, the concentration of sodium in the cross section of pure sodium alginate film and sodium alginate/ Eudragit® L 30 D-55 mixture films before and after acid treatment was determined using scanning electron microscopy/energy dispersive X-ray spectroscopy (SEM/EDX). 10% sodium was present in the original pure sodium alginate film (Table 2.7). The amount of sodium ions in sodium alginate/ Eudragit® L 30 D-55 mixture films were 3.3%, 1.8% and 1.0% in the cross-section of the films containing 50%, 20% and 10% sodium alginate respectively. After 2 hours exposure to pH 1.2 HCl, almost all of the sodium ions in the pure sodium alginate film and the mixture films were lost, due to ion exchange in the acidic medium. These results could explain that after 2 hour acid treatment, the sodium alginate/ Eudragit® L 30 D-55 mixture film did not dissolve faster in buffer due to the leakage of sodium ions in acid medium. Interestingly however, although sodium ions in the pure sodium alginate film also leached out in pH 1.2 HCl, the film dissolution was still fast in subsequent buffer. This indicates that the presence of sodium ions in the pure sodium alginate film was not the only reason for the fast film dissolution in buffer.
Table 2.6. Sodium concentration in films before and after acid treatment

<table>
<thead>
<tr>
<th>Sodium concentration (% mass)</th>
<th>Pure sodium alginate film</th>
<th>Eudragit® L 30 D-55/sodium alginate film (sodium alginate concentration)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>50%</td>
<td>20%</td>
</tr>
<tr>
<td>Before acid treatment</td>
<td>9.3</td>
<td>3.3</td>
</tr>
<tr>
<td>After 2 hour in pH 1.2 HCl</td>
<td>0.1</td>
<td>&lt;0.1</td>
</tr>
</tbody>
</table>

To further understand the compatibility of sodium alginate to Eudragit® L 30 D-55 film, an EDX-mapping analysis was conducted with 50% sodium alginate-containing film and showed that sodium alginate is not homogeneously distributed in Eudragit® L 30 D-55 film. Figure 2.24 shows the sodium and carbon distribution in the same area of SEM image of 50% sodium alginate-containing film. In some areas (10 – 20 μm), sodium ion (from sodium alginate) is depleted and in the corresponding area, carbon (from Eudragit® L 30 D-55) is enriched.

![Figure 2.24. Sodium and carbon distribution in the cross-section of 50% sodium alginate-containing Eudragit® L 30 D-55 film.](image-url)
SEM images of the cross-sections of the film also show that pure sodium alginate forms a very smooth and homogenous film (Figure 2.25). However, the sodium alginate/ Eudragit® L 30 D-55 mixture film is not homogenous with recognizable oval areas (diameter ~ 10 – 20 µm) in the film. These results indicate that sodium alginate is not miscible with Eudragit® L 30 D-55 film. This incompatibility could be the main reason of the lack of acceleration of the Eudragit® L 30 D-55 film dissolution by the incorporation of sodium alginate.

![Figure 2.25. Scanning electron micrographs of the cross-section of the pure sodium alginate film and the 50% sodium alginate-containing Eudragit® L 30 D-55 film.](image)

2.10 CONCLUSION

Low molecular weight organic acids and high molecular weight polymers, with pH-sensitive properties, were included in Eudragit® L 100-55 and Eudragit® L 30 D-55 films. However it was not feasible to accelerate the dissolution of Eudragit® films in buffer after acid treatment by the incorporation of these materials. For Eudragit® L 100-55 film, the incompatibility of the film with organic acids having low water solubility, such as sorbic acid and fumaric acid resulted in their lack of
assistance in film dissolution. Organic acids with high water solubility, such as citric, succinic and adipic acids leached out from the films in acid medium and thus were not able to accelerate the film dissolution in buffer.

Organic acid-containing partially neutralized Eudragit® L 30 D-55 films showed very fast dissolution rate when directly testing in buffer due to the dissociation and ionization of the polymer by partial neutralization. However when testing these films in acid medium, the high acidity of HCl caused ion exchange between the medium and the sodium salt of the polymer. The resultant acid form of the polymer therefore showed no accelerated dissolution in subsequent buffer.

On mixing with pectin and xanthan solution, the film formation process of Eudragit® L 30 D-55 dispersion was altered, resulting in incomplete particle deformation and coalescence. This, together with the high hydrophilicity of pectin and xanthan, induced the leaching of these polymers from the film in acid medium. Alginic acid was not able to assist in the film dissolution due to its slow dissolution in buffer. SEM/EDX analysis showed that sodium alginate was not homogeneously mixed with Eudragit® L 30 D-55 film and sodium ions were exchanged by the acid medium during acid treatment. This caused the slow dissolution of sodium alginate-containing film.

Although the acceleration of the Eudragit® film dissolution in small intestinal conditions was not achieved by the above approaches, some interesting findings were obtained and shed light for the following step of the research. The very high dissolution rate of organic acid-containing partially neutralized Eudragit® L 30 D-55 film in direct buffer was desirable for the acceleration of the film dissolution. However, this fast film dissolution could not be maintained after acid treatment due to the ion exchange. It was therefore of value to explore potential approaches to protect the necessary properties of these films in acid medium to preserve the fast dissolution performance in subsequent buffer.
CHAPTER 3

POTENTIAL FOR A DOUBLE-COATED SYSTEM TO ACCELERATE THE DISSOLUTION OF ENTERIC COATINGS
3.1 INTRODUCTION

In an attempt to achieve fast film dissolution in upper small intestinal conditions, organic acids and pH-sensitive polymers were incorporated into Eudragit® L 30 D-55 and Eudragit® L 100-55 films. The film dissolution in subsequent buffer was not accelerated by the inclusion of these additives after 2 hours exposure to pH 1.2 HCl, due to either the leaching of the water soluble additives or the ionic exchange in acid medium. However, some of these formulations, especially partially neutralized Eudragit® L 30 D-55 films containing organic acids showed a positive influence on film dissolution properties when directly testing in buffer.

Polymer particles in Eudragit® L 30 D-55 dispersion completely dissolved when the dispersion was neutralized to pH 5.6 using 1 M NaOH in the presence of organic acids, such as adipic acid. Since the methacrylic acid groups of the polymer were partially ionized in this formulation, the water insoluble Eudragit® L 30 D-55 was changed to a water soluble polymer. Films cast from this organic acid-containing partially neutralized Eudragit® L 30 D-55 solution dissolved very fast in pH 6.0 phosphate buffer (completely dissolved within 5 minutes); whereas it took 2 hours for the non-neutralized control Eudragit® L 30 D-55 film to dissolve completely at the same buffer pH. However, after exposure to pH 1.2 HCl for 2 hours, the film dissolution performance in subsequent buffer showed no difference compared to the control film. SEM/EDX tests illustrated that upon exposure to acid medium, the sodium salt of Eudragit® L 30 D-55 polymer, formed by the addition of NaOH, was converted back to the acid form, and thus leading to the slow dissolution in subsequent buffer.

The exposure to acidic conditions in the stomach is inevitable for enteric-coated dosage forms before dissolving in the small intestine. Therefore, these organic acid-containing partially neutralized Eudragit® L 30 D-55 films are not sufficient to fulfil the task - fast dissolution in small intestinal conditions, unless the functional
properties of the film could be protected in acid medium. A conceivable way to protect the film in acid medium would be to apply a normal enteric coating, such as Eudragit® L 30 D-55, on top of the neutralized film coat. Theoretically, the polymer salt in the partially neutralized coating layer can be kept after the treatment in acid medium, due to the protection of the outer enteric coating. However, would this double-coated (obviously thicker) system dissolve faster than the normal enteric coating (single-layer, as shown in Figure 3.1) in subsequent small intestinal conditions?

Figure 3.2 demonstrates the concept of the Eudragit® L 30 D-55 double coating system. Substrate cores first were coated with the organic acid-containing partially neutralized Eudragit® L 30 D-55 solution and then over-coated with a normal Eudragit® L 30 D-55 coating. To answer the above question regarding the dissolution of this double coating in buffer, an assumption needs to be made that buffer solution can diffuse through the outer coat before the outer coat starts to dissolve. As implicated by the free film study, the partially neutralized inner coat dissolves very fast upon contact with the buffer solution. Again, another assumption is that the functional properties of the inner coat which renders its fast dissolution in buffer, such as the presence of sodium ions, are also able to assist the dissolution of the outer coat. Thus, the dissolution rate of the whole double coating system could possibly be accelerated.
Figure 3.1. Demonstration of the normal single-layer enteric coating (*Eudragit L* 30 D-55 was used as an example).

Figure 3.2. Demonstration of the double coating system.
The potential of applying a Eudragit® L 30 D-55 double-coated system for the purpose of fast drug release in upper small intestinal conditions was investigated in this phase of the study. The acid-resistant properties of the double-coated system were tested by applying the double coating on prednisolone tablets. Drug release from the double-coated prednisolone tablets was determined in buffer solutions resembling upper small intestinal pH conditions and compared with the normal single layer Eudragit® L 30 D-55 coated (control-coated) tablets.

In addition to conventional drug release studies, other techniques were also employed to understand the coat dissolution properties of the double-coated system compared to the control coating. The dissolution velocities of Eudragit® L 30 D-55 polymer from the double-coated and the control-coated systems were determined using refractive index detection by applying on placebo glass beads. Confocal laser scanning microscopy (CLSM) was used to reveal the coating dissolution processes of the double coating and the control coating by using prednisolone pellets and the results were correlated to drug release results from these coated pellets.

After establishing the dissolution performance of the double-coated system, the system was then optimized by investigating the influence of different formulation factors, such as outer coat thickness, acid species/concentrations in the inner coat and the inner coat neutralization values, on drug release.
SECTION 1: IN VITRO DRUG RELEASE FROM DOUBLE-COATED PREDNISOLONE TABLETS

3.2 INTRODUCTION

In Chapter 2, adipic acid has been used to accelerate the dissolution of partially neutralized Eudragit® L 30 D-55 film in buffer and the result was satisfactory. Therefore, the potential of including adipic acid in the inner coat of the double-coated formulation for rapid drug release was investigated in the present study. The influence of using citric acid, which has higher water solubility than adipic acid, in the inner coat on drug release was also investigated.

Acid-resistance tests of the double-coated formulations were conducted in more strict conditions than commonly used testing methods to take into account the realities of gastric emptying and gastric pH conditions. Acid-resistance tests for enteric-coated products are normally carried out in pH 1.2 HCl or simulated gastric fluid (pH 1.2) for 2 hours. However, these tests do not necessarily ensure the integrity of enteric-coated products in the stomach if the gastric emptying is delayed or the dosage form encounters high gastric pH conditions. This has been discussed in detail in Chapter 1. Therefore, it is necessary to test the acid-resistance of enteric-coated products for longer time and in acid solutions with higher pH values than normal in vitro test conditions.

Drug release tests were also carried out in buffer solutions with pH values better resembling upper small intestinal pH conditions compared to the commonly used dissolution media. Unlike pH 6.8, used for current in vitro tests, the pH values in the duodenum and the proximal jejunum are relatively low, pH 5.0-6.2 (Rune and Viskum, 1969; Benn and Cooke, 1971; Ovesen et al., 1986; Fallingborg et al., 1989;
Dressman et al., 1990; Fallingborg et al., 1994), and gradually increase toward the distal part of the small intestine. Therefore, instead of the pH 6.8 phosphate buffer, phosphate buffer solutions with pH values from 5.0 to 6.2 were used for drug release tests from the double-coated and the control-coated tablets. The implications of the in vitro dissolution performance in these low pH buffers on the in vivo performance of the coated dosage forms are also discussed.

3.3 MATERIALS

Prednisolone was purchased from Aventis Pharma., Antony, France. Lactose (Pharmatose, 110µm) was purchased from Ellis & Everard, Essex, UK. Sodium carboxymethylcellulose (Ac-di-sol) was donated by FMC International, Cork, Eire. Polyvinylpyrrolidone (PVP) was purchased from VWR International Ltd, Poole, UK. Magnesium stearate was purchased from Sigma St. Louis, MO, USA. Eudragit® L 30 D-55 was donated by Röhm GmbH, Darmstadt, Germany. Triethyl citrate (TEC) was purchased from Lancaster Synthesis, Lancashire, UK. Talc (fine powder) was purchased from VWR International Ltd, Poole, UK. All other reagents were purchased from Sigma, St. Louis, MO, USA. De-ionized water was used.

Rationale for model drug

Prednisolone was used as the model drug for enteric coating in this study. The chemical structure of prednisolone is shown in Figure 3.3.
Figure 3.3. Chemical structure of prednisolone (Molecular weight: 360.4; Log P: 1.7).

Prednisolone is a corticosteroid. The predominant activity of prednisolone is glucocorticoid and mineralocorticoid activity is low. Prednisolone is used for the treatment of a wide range of inflammatory and auto-immune conditions, including asthma, rheumatoid arthritis, multiple sclerosis, ulcerative colitis and Crohn's disease. The main side effect of prednisolone, as with other glucocorticoids, is Cushing’s syndrome. Oral administration of prednisolone is usually in the form of enteric-coated products to overcome the gastric irritation by the drug.

The main reasons for prednisolone to be a suitable model drug for enteric coating are its relatively low water solubility (2.225 g/L) (Yalkowsky and He, 2003), and that it is a neutral molecule. Active substances which have high water solubility can alter the acid-resistant properties of the enteric coating and drug release can take place by diffusion before the coat dissolution (Guo et al., 2002a). Acidic or basic drugs in the core can influence the dissolution of the pH-dependent enteric coating, by changing the microenvironment pH of the coat (Dressman and Amidon, 1984; Crotts et al., 2001). Therefore, the use of prednisolone as a model drug can eliminate the influence of the core properties on the dissolution of enteric coatings, and thus better discriminate the performance of different coating formulations.
3.4 METHODS

3.4.1 Preparation of prednisolone tablets

Prednisolone tablets were prepared by wet granulation. Each tablet contains 5% prednisolone (10 mg), 88.5% lactose, 5% PVP, 0.5% Ac-di-sol and 1% magnesium stearate.

Prednisolone was dry blended with lactose, PVP and half of the Ac-di-sol for 15 minutes using a planetary mixer (model A707A, Kenwood, Hampshire, UK), followed by drop wise addition of water under continuous mixing until a homogenous wet mixture was obtained. The wet mixture was then granulated by passing through a 710 µm mesh size sieve. The obtained wet granules were then dried in a 60 °C oven until the weight was constant. Upon drying the granules were passed through 710 µm sieve to remove aggregates and then passed through 90 µm sieve to remove fine powder. The rest of the Ac-di-sol was then added to the granules in an amber glass jar and roller-mixed for about 10 minutes, followed by mixing with 1% magnesium stearate in the same way for 5 minutes.

Tablets were produced using a single punch tableting machine (Manesty, Speke, UK), fitted with a biconvex 8 mm punch and die set (Holland, Nottingham, UK) to obtain the tablet weight of 200 mg and crushing strength of 80 N.

3.4.2 Coating of prednisolone tablets with Eudragit® L 30 D-55 formulations

Three coating formulations were applied on prednisolone tablets, a control coating and two double coating formulations:

*Control coating:* Eudragit® L 30 D-55 single coating, 5mg/cm²;
Double coating (adipic acid): inner coat – Eudragit® L 30 D-55 neutralized to pH 5.6 in the presence of 10% adipic acid, 5mg/cm²; outer coat – Eudragit® L 30 D-55, 5mg/cm².

Double coating (citric acid): inner coat – Eudragit® L 30 D-55 neutralized to pH 5.6 in the presence of 10% citric acid, 5mg/cm²; outer coat – Eudragit® L 30 D-55, 5mg/cm²;

3.4.2.1 Preparation of coating dispersions

Organic acid-containing Eudragit® L 30 D-55 inner coat:
Adipic acid and citric acid, respectively, (10%, based on polymer weight), and 5% triethyl citrate (TEC) (based on polymer weight) were dissolved in water, and added into Eudragit® L 30 D-55 dispersions. The above dispersions were then neutralized to pH 5.6 using 1 M NaOH and the dispersions turned to clear solutions. Fifty percent talc (based on polymer weight) was homogenized in water and added to above solutions. The amount of water in the formulation was calculated to obtain a 10% total solid content of the coating dispersion.

Eudragit® L 30 D-55 control and outer coat:
The same composition of coating dispersion was used for the control coating and the outer coat of the double coating. Ten percent TEC (based on polymer weight) was dissolved in water, and added into Eudragit® L 30 D-55 dispersion. Fifty percent talc (based on polymer weight) was homogenized in water and added into the above dispersion. The amount of water in the formulation was calculated to obtain a 10% total solid content of the coating dispersion.
3.4.2.2 Film coating for prednisolone tablets

The tablets (40g for each batch) were coated using Strea-1 bottom spray fluidized bed spray coater (Aeromatic AG, Bubendorf, Switzerland). The coating conditions for each formulation are shown in Table 3.1.

### Table 3.1. Coating conditions of different coating formulations for tablets

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Inlet air temperature (°C)</th>
<th>Outlet air temperature (°C)</th>
<th>Capacity of fan</th>
<th>Atomizing pressure (bar)</th>
<th>Flow rate (ml/minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organic acid-containing inner coat</td>
<td>40</td>
<td>30</td>
<td>15</td>
<td>0.2</td>
<td>0.5-1.5</td>
</tr>
<tr>
<td>Control and outer coat</td>
<td>40</td>
<td>30</td>
<td>15</td>
<td>0.2</td>
<td>2.0</td>
</tr>
</tbody>
</table>

In the literature, percentage weight gain is commonly used to control the coating thickness of enteric-coated products (Gordon et al., 1995; Guo et al., 2002b). However, it was not possible to directly compare the amount of enteric polymer applied on the coat between different studies by using the percentage weight gain. This is due to the different amount of additives in the formulations and the different shape of the cores, especially between tablets and pellets. In the present study, to achieve the comparable enteric properties for different formulations, the coating thickness was controlled by applying a certain amount of dry polymer substance (Eudragit® L 30 D-55) on per cm² of tablet surface. The same method was also applied by other research groups (Schmidt and Niemann, 1992; Cole et al., 2002). Based on the manufacturer’s recommendation of 4-6 mg/cm² to provide gastric resistance for Eudragit® L 30 D-55 enteric-coated tablets (Technical Bulletin, 2005, Degussa Röhm Pharma Polymers), the amount of polymer applied on the control
coating and the inner and outer coat of the double coating were chosen as the same value: 5mg/cm².

The percentage total weight gain was still used to control the coating process time; however, it was calculated based on the desired polymer quantity on the final coat. To calculate the percentage total weight gain, firstly, the percentage of polymer weight gain by tablet (coating weight %) was calculated as follows:

\[
\text{Coating weight (\%)} = \frac{A(\text{mm}^2) \cdot I(\text{mg/cm}^2)}{w(\text{mg})}
\]

\(A(\text{mm}^2)\): Surface area per tablet;
\(I(\text{mg/cm}^2)\): mg of polymer per cm² of tablet surface;
\(w(\text{mg})\): Weight of one tablet.

The total weight gain (weight gain %) by tablet was then calculated:

\[
\text{Weight gain (\%)} = \text{coating weight (\%)} \cdot \frac{w_s(g)}{w_p(g)}
\]

\(w_s(g)\): total solid weight in the coating formulation;
\(w_p(g)\): dry polymer weight in the coating formulation.

The surface area of tablet was calculated using the following formula:

\[
A(\text{mm}^2) = \pi \cdot (D \cdot H + 0.5 \cdot D^2)
\]

\(D(\text{mm})\): diameter of tablet;
\(H(\text{mm})\): height of tablet.
Coating process was continued until the required total weight gain was achieved. After each coating run, tablets were fluidized for a further 15 minutes to allow the coat to dry.

3.4.3 Scanning electron microscopy

The surfaces and cross-sections of the control-coated and the double-coated prednisolone tablets were examined by scanning electron microscopy (SEM), using a JEOL JSM-35 Scanning Microscope. The electron energy applied was 5-10 keV. Samples were gold coated using a EMITEC K500 sputter coater for three minutes at 40 mA. The inner coat (first coat) surfaces of the double-coated tablets were examined before the application of the outer coat. The film thickness of the control coating and the double coating (10% citric acid) on tablet surface was determined using SEM. The test was conducted in triplicate.

3.4.4 In vitro drug release testing

The drug release profiles from the coated prednisolone tablets were carried out using a BP Method II paddle apparatus (Model PTWS, Pharmatest, Hainburg, Germany). The tests were conducted at least in triplicate, in 900 ml dissolution medium maintained at 37 ± 0.5 °C. A paddle speed of 50 rpm was employed. The amount of prednisolone released from the coated tablets was determined at 5 minutes intervals by an in-line UV spectrophotometer at a wavelength of 247 nm. Tablets were placed for 2 hours into pH 1.2 HCl, and subsequently into pH 5.0, 5.5, 5.6, 5.8, 6.0 and 6.2 phosphate buffer.

1000 ml of phosphate buffer solutions (0.067M) with different pH values were prepared by mixing different amounts of two stock solutions, depending on the pH value listed in Table 3.2. The pH of the buffer was adjusted to the desired value using 2% H₃PO₄ or 1 M NaOH, if necessary.
Stock solution I: 18.4 g NaH$_2$PO$_4$.H$_2$O dissolved in 2000 ml water

Stock solution II: 23.9 g Na$_2$HPO$_4$.2H$_2$O dissolved in 2000 ml water

<table>
<thead>
<tr>
<th>pH value of the buffer solution</th>
<th>Stock solution I (ml)</th>
<th>Stock solution II (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.0</td>
<td>1000</td>
<td>0</td>
</tr>
<tr>
<td>5.5</td>
<td>960</td>
<td>40</td>
</tr>
<tr>
<td>5.6</td>
<td>940</td>
<td>60</td>
</tr>
<tr>
<td>5.8</td>
<td>920</td>
<td>80</td>
</tr>
<tr>
<td>6.0</td>
<td>880</td>
<td>120</td>
</tr>
<tr>
<td>6.2</td>
<td>840</td>
<td>160</td>
</tr>
</tbody>
</table>

3.5 RESULTS AND DISCUSSION

3.5.1 Scanning electron micrographs of the control-coated and the double-coated tablets

Prednisolone tablets were coated with the control Eudragit® L 30 D-55 coating (single layer) and two double coating formulations with 10% adipic acid and 10% citric acid in the inner coat respectively. The scanning electron micrographs of the surface and cross-sections of the control-coated and the double-coated tablets are shown in Figure 3.4.
Figure 3.4. Scanning electron micrographs of the surface and cross-section of the control-coated and the double-coated tablets.
The coating thicknesses on the tablet surface were 86.1± 5.9 μm and 186.1± 8.4 μm for the control coating and 10% citric acid double coating respectively. The inner coat surfaces of the double-coated formulations were examined before the outer coat was applied. The adipic acid-containing inner coat showed a smoother surface than the citric acid-containing inner coat. From the cross-section of the double-coated tablets, the difference of the inner coat and the outer coat could be seen. The inner coat formed a tighter film compared to the outer coat, due to the application of the polymer solution instead of dispersion. The surface of the outer coat of the two double-coated formulations showed the same feature as the surface of the control coating (images not shown).

3.5.2 Acid-resistance tests

Acid-resistance tests were carried out for extended periods of time in pH 1.2 HCl (21 hours), far in excess of the normal gastric emptying time. There was no drug release from the control-coated or the double-coated (10% adipic acid) prednisolone tablets in this condition for 21 hours. In addition, the control-coated and the double-coated prednisolone tablets were placed in pH 2.0, 3.0 and 4.0 HCl solutions for 3 hours, and both showed no drug release. The results of these acid-resistance tests indicate that the double-coated formulation has good gastric resistance.
3.5.3 Comparison of drug release from the double-coated and the control-coated prednisolone tablets in different buffer pH

Figures 3.5 – 3.10 show the comparison of drug release from prednisolone tablets coated with the two double coating formulations and the control coating at pH 5.0, 5.5, 5.6, 5.8, 6.0 and 6.2 phosphate buffer following 2 hours exposure to pH 1.2 HCl. The dissolution pH threshold of Eudragit® L 30 D-55 polymer is 5.5; therefore it was not surprising that there was no drug release from the control-coated tablets at pH 5.0 for 6 hours (Figure 3.5). The drug release from the control-coated tablets at pH 5.5 and 5.6 was very slow (Figures 3.6 and 3.7), which agrees with the drug release results reported by Huyghebaert et al. (2005), in which thymidine (model drug) released very slowly from Eudragit® L 30 D-55 coated pellets in pH 5.5 phosphate buffer. However, when increasing the buffer pH from 5.6 to 5.8, a dramatic increase in drug release rate was seen (Figure 3.8).

Figure 3.5. Drug release profiles of the Eudragit® L 30 D-55 double-coated and the control-coated prednisolone tablets in pH 5.0 phosphate buffer after pre-treatment in pH 1.2 HC for 2 hours.
Figure 3.6. Drug release profiles of the Eudragit® L 30 D-55 double-coated and the control-coated prednisolone tablets in pH 5.5 phosphate buffer after pre-treatment in pH 1.2 HCl for 2 hours.

Figure 3.7. Drug release profiles of the Eudragit® L 30 D-55 double-coated and the control-coated prednisolone tablets in pH 5.6 phosphate buffer after pre-treatment in pH 1.2 HCl for 2 hours.
Figure 3.8. Drug release profiles of the Eudragit® L 30 D-55 double-coated and the control-coated prednisolone tablets in pH 5.8 phosphate buffer after pre-treatment in pH 1.2 HCl for 2 hours.

Figure 3.9. Drug release profiles of the Eudragit® L 30 D-55 double-coated and the control-coated prednisolone tablets in pH 6.0 phosphate buffer after pre-treatment in pH 1.2 HCl for 2 hours.
Control coating
Double coating: 10% adipic acid
Double coating: 10% citric acid

Figure 3.10. Drug release profiles of the Eudragit® L 30 D-55 double-coated and the control-coated prednisolone tablets in pH 6.2 phosphate buffer after pre-treatment in pH 1.2 HCl for 2 hours.

In all of the test pH, tablets coated with the two double coating formulations (10% adipic acid and 10% citric acid formulations) showed faster drug release than the control-coated tablets. It is of note that there was about 20-40% drug release from double-coated tablets after 6 hours in pH 5.0 buffer (Figure 3.5). In contrast to the very slow drug release from the control-coated tablets at pH 5.5 and 5.6, the double-coated tablets showed considerably faster drug release at these low pH values (Figures 3.6 and 3.7). At pH 5.8, the double-coated tablets also showed substantial acceleration of drug release compared to the control-coated tablets, with the lag times of 60, 35 and 25 for the control-coated, 10% adipic acid double-coated and 10% citric acid double-coated tablets, respectively (Figure 3.8). However, the differences in drug release rate between the double-coated and the control-coated tablets reduced with increasing media pH. The double-coated tablets still showed faster drug release profiles than the control-coated tablets at pH 6.0 (Figure 3.9). At pH 6.2, drug release was very fast for all of the coating formulations, thus showing
no difference between the control-coated and the double-coated tablets (Figure 3.10).

It is to be noted that only phosphate buffers in the lower pH range (pH 5.0-6.0) could discriminate the difference in drug release between the double-coated and the control-coated tablets. Huyghebaert et al. (2005) also showed that only in phosphate buffers ranging from pH 5.5 to 6.0, the difference of drug release from Eudragit® L 30 D-55 coated pellets with different coating thicknesses (10%, 15%, 20% and 30%) were seen. At pH 6.5, increasing the coating thickness did not affect the release rate. Similar trend was also reported for tablets coated with different Eudragit® polymers having the same dissolution pH threshold of 7.0 (Eudragit® S aqueous, Eudragit® S organic and Eudragit® FS); only in phosphate buffer with relatively low pH (7.0-7.2), the difference of drug release between different coating formulations is evident (Ibekwe et al., 2006a).

The acceleration of drug release from the double-coated formulations in lower pH values has implications on the in vivo behaviour of these formulations. The in vitro assessment of drug release from enteric-coated dosage forms is usually conducted by dissolution testing in pH 6.8 phosphate buffer, despite that polymers used for enteric coating normally start to dissolve at pH below 6.0. The dissolution speeds of the enteric polymers are already high at pH 6.8, and thus, it is not possible to differentiate the dissolution behaviour between different enteric-coated formulations (Bianchini et al., 1991). However, these enteric coatings do not always exhibit the same in vivo performance, with disintegration times varying from 20 minutes to 2 hours post gastric emptying (Bogentoft et al., 1984; Hardy et al., 1987; Wilding et al., 1993; Ebel et al., 1993; Cole et al., 2002). In the study by Ibekwe et al. (2006a), the difference of drug release between Eudragit® FS, Eudragit® S aqueous and Eudragit® S organic coated tablets was not able to be recognized in pH 7.4 phosphate buffer, which is commonly used for testing pH-responsive colonic delivery dosage forms. However, the in vivo scintigraphy study showed distinct
tablet disintegration times and positions for these three coating formulations (Ibekwe et al., 2006b).

The different *in vivo* performance of enteric polymers is likely due to the different dissolution behaviour of these polymers at lower pH values. It is known that intestinal pH is not always as high as pH 6.8. The duodenum pH is around pH 5.0 to 6.2, and gradually increases to pH 6.5 to 7.0 in the distal small intestine (Evans et al., 1988; Fallingborg et al., 1989; Dressman et al., 1990; Fallingborg, 1999; Nugent et al., 2001). Even if the contact time with the lower pH fluid in the small intestine is not long enough to disintegrate the enteric-coated dosage forms, the differences of the film dissolution level and the film permeability at these lower pH values would influence the eventual disintegration time of the coated dosage forms.

Figures 3.5-3.10 also compared the drug release from 10% citric acid and 10% adipic acid double-coated tablets. 10% citric acid formulation showed faster drug release rates than 10% adipic acid formulation. These results can help to further optimize the double coating formulation and to understand the function of organic acids in the double coating system.
3.6 INTRODUCTION

*In vitro* drug release testing is commonly used to assess the dissolution properties of film coated pharmaceutical dosage forms and to predict the *in vivo* performance. However, drug release from film coated products is not only the result of the coat dissolution. It can also take place due to drug diffusion through the film by different routes, including the openings between cross-linked polymer chains, plasticizer channels or aqueous pores (Ozturk et al., 1990). Therefore, drug release does not always represent the dissolution properties of the film coating. Determination of polymer dissolution velocities from film coatings could provide a direct comparison of dissolution properties of different coating formulations, and therefore, help to better understand the mechanisms involved in the dissolution. Very limited work has been done on this comparative testing with enteric polymers. Davis et al. (1986a) compared the dissolution rates of free films cast from three types of enteric polymers in different buffer pH. The polymers tested were cellulose acetate phthalate (CAP), polyvinyl acetate phthalate (PVAP) and hypromellose phthalate (HP-50 and HP-55). The authors found that the difference of dissolution rates between polymers of the same type was associated to the pKₐ values of the polymer (i.e. HP-50 and HP-55), whereas variation in the backbone structure of different types of polymer was the primary reason for the differences in their dissolution rates.

For direct comparison of the dissolution properties of the double-coated and the control-coated formulations, the polymer dissolution velocities of these two types of formulation were determined in this section of the study. Previous researchers used
free polymeric films for testing polymer dissolution velocities; however, in the present study, film coated placebo glass beads were applied to give a better correlation to the *in vitro* drug release testing. UV spectrophotometry was used by Davis et al. (1986a) to determine the dissolution rates of above mentioned phthalate-based enteric polymers. Since Eudragit® L 30 D-55 does not have UV absorbance, it is not possible to determine the amount of polymer dissolved from the coated glass beads using UV spectrophotometry. To determine the dissolution rates of Eudragit® polymers, a pH-stat titration method was described in the literature (Spitael and Kinget, 1977a). Polymer film was immersed in buffer solution and once the polymer dissolution started, 0.5 M NaOH was automatically added into the solution to compensate the acidity of the polymer and maintain the solution at a given pH. The amount of polymer dissolved was calculated from the amount of 0.5 M NaOH consumed. However, since the inner coat of the double-coated formulation was already neutralized using 1 M NaOH, upon dissolution the alkaline in the inner layer will also contribute to the titration of the polymer and therefore give inaccurate titration results.

In the present study, refractive index detection which offers a universal response to the testing sample was chosen as the technique to determine the amount of Eudragit® L 30 D-55 polymer dissolved from the double-coated and the control-coated glass beads. The refractive index detector monitors the deflection of a light beam caused by the refractive index difference between the contents of the sample cell and that of the reference cell. It is thus used for testing compounds that do not have strong UV chromophores, fluorophores, electrochemical or ionic activities.
3.7 MATERIALS

Placebo glass beads (spherical, 5mm diameter) were purchased from Peco Laborbedarf GmbH, Darmstadt, Germany. Eudragit® L 30 D-55 was donated by Röhm GmbH, Darmstadt, Germany. Triethyl citrate (TEC) was purchased from Lancaster Synthesis, Lancashire, UK. Talc (fine powder) was purchased from VWR International Ltd, Poole, UK. All other reagents were purchased from Sigma, St. Louis, MO, USA. De-ionized water was used.

3.8 METHODS

3.8.1 Coating of glass beads with Eudragit® L 30 D-55 formulations

3.8.1.1 Preparation of coating dispersions

Two coating formulations were applied on glass beads, a double coating formulation and a control coating formulation.

*Control coating:* Eudragit® L 30 D-55 single coating, 5mg/cm²;

*Double coating:* inner coat – Eudragit® L 30 D-55 neutralized to pH 5.6 in the presence of 10% citric acid, 5mg/cm²; outer coat – Eudragit® L 30 D-55, 5mg/cm²;

Organic acid-containing Eudragit® L 30 D-55 inner coat and Eudragit® L 30 D-55 control and outer coat formulations were prepared using the method described in Section 3.4.2.1.
3.8.1.2 Film coating for glass beads

Glass beads (150 g for each batch) were coated using Hüttiln Mycrolab bottom spray fluidized bed spray coater (Hüttiln GmbH, Steinen, Germany). The coating conditions for each formulation are shown in Table 3.3.

Table 3.3. Coating conditions of different coating formulations for glass beads

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Inlet air temperature (°C)</th>
<th>Product temperature (°C)</th>
<th>Exhaust air temperature (°C)</th>
<th>Airflow (m³/h)</th>
<th>Atomizing air pressure (bar)</th>
<th>Spray rate (g/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organic acid-containing</td>
<td>35</td>
<td>30</td>
<td>25</td>
<td>27</td>
<td>1.2</td>
<td>1.0</td>
</tr>
<tr>
<td>inner coat</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control and outer coat</td>
<td>33</td>
<td>30</td>
<td>28</td>
<td>26</td>
<td>1.5</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Coating processes were controlled by the total weight gain, which was calculated based on the desired polymer quantity on the coat. The method for calculating the total weight gain was described in Section 3.4.2.2. The surface area of glass beads was calculated using the following formula:

\[ A \ (mm^2) = \pi \cdot D^2 \]

\( D \ (mm) \): Diameter of bead.

Coating process was continued until the required total weight gain was achieved. After each coating run, glass beads were fluidized for a further 15 minutes to allow the coat to dry.
3.8.2 Polymer dissolution velocity tests on coated glass beads

3.8.2.1 Testing process

The schematic picture of the apparatus used for measuring the polymer dissolution velocities are shown in Figure 3.11. A heat-jacketed glass vessel (volume 175 ml) was filled with 150 ml of buffer solution preheated to 37 ± 0.5 °C. Coated glass beads (weight equivalent to 0.2 g polymer for the control-coated formulation and 0.4 g polymer for the double-coated formulation) were put into a glass tube (basket) (2 cm internal diameter, 14 cm height) with perforated bottom (hole size 1 mm). The glass tube was then put into the buffer solution in the vessel and immediately set in motion (up and down, at 29-32 cycles per minute) by a USP disintegration test engine. With a magnetic stirrer, buffer solution was stirred continuously with a speed of 400 rpm. Samples of the buffer solution were continuously withdrawn out of the vessel through a Teflon filter (10 μm pore size, Pharmatest, Hainburg, Germany) with a speed of 1 ml per minute. After passing through a refractive index detector (RI-detector, model 8120, Bischoff Analysentechnik & Geräte GmbH, Leonberg, Germany), samples were then refilled into the test vessel. The amount of polymer dissolved from the coated glass beads was determined at 5 seconds intervals by RI-detector. The signals of RI-detector (in the unit of mV) were exported via a recorder with an output of 0-100mV.
Figure 3.11. Schematic picture of the apparatus for measuring the polymer dissolution velocities (with permission from Röhm GmbH, Darmstadt, Germany).

After the film coating started to dissolve, the pH value of the buffer solution dropped due to the dissolution of the acidic polymer. To overcome the pH decrease of the buffer solution, a titration system (Mettler titrator Type DL77, Mettler-Toledo GmbH, Greifensee, Switzerland) was connected to the test vessel, and the buffer solution was automatically titrated using 0.5 M NaOH at 20 seconds intervals to maintain the constant pH value.

Phosphate buffer solutions with pH values of 4.0, 4.5, 5.0, 5.5, 5.8, 6.0 and 6.2 were used for the polymer dissolution velocity tests and prepared using the formula reported in Section 3.4.4. Buffer solutions of pH 4.0 and 4.5 were prepared by adjusting the pH of the stock solution I (as described in Section 3.4.4) using 0.5 M HCl. Coated glass beads were placed in pH 1.2 HCl for 2 hours before tested in buffer. Single test was conducted in each buffer pH.
3.8.2.2 Calibration curve for RI-detector

A calibration curve was conducted to transfer the RI-detector signal (mV) to the polymer concentration (mg/ml) in the buffer solution. Eudragit® L 30 D-55 was dissolved in pH 6.2 phosphate buffer to obtain a series of polymer concentrations of 0.5, 1.0, 1.5, 2.0, 3.0 mg/ml. Ten percent TEC and 50% talc (both based on the polymer weight) were added into the solution to obtain the same proportion to the polymer as in film coating. The RI-detector signals of these polymer solutions were recorded to plot a calibration curve of mV-mg/ml. The resultant calibration curve was linear in this polymer concentration range \( y = 16.27x \), correlation coefficient 0.997. Since the signals of RI-detector for Eudragit® L 30 D-55 at different buffer pH were constant, the calibration curve at pH 6.2 was used for all of the buffer pH values.

3.8.2.3 Calculation of polymer dissolution velocities

The percentage of polymer dissolved into buffer solution was calculated using the following formula:

\[
A(\%) = \frac{R(mV) \cdot V(ml) \cdot 100}{w_1(mg) \cdot w_2(g) \cdot E(mV \cdot ml/mg)}
\]

\( A(\%) \): percentage of polymer dissolved;
\( R(mV) \): signal of RI-detector;
\( V(ml) \): volume of dissolution medium (150 ml);
\( w_1(mg) \): weight of glass beads;
\( w_2(g) \): [g] polymer on 1 g glass beads;
\( E(mV \cdot ml/mg) \): slope of calibration curve.
The curves of percentage of polymer dissolved by time (% - minutes) were plotted. The slopes of the linear part of the curves were used as the polymer dissolution velocities (%/minute) at different buffer pH.

3.9 RESULTS AND DISCUSSION

3.9.1 Comparison of polymer dissolution velocities from the control-coated and the double-coated glass beads in different buffer pH

Figure 3.12 shows the dissolution velocities of Eudragit® L 30 D-55 from the double-coated glass beads with 10% citric acid in the inner coat and the control-coated glass beads in phosphate buffers with pH values ranging from 4.0 to 6.2, following acid exposure for 2 hours. Eudragit® L 30 D-55 started to dissolve from the control-coated glass beads at pH 5.5 and the dissolution velocity increases with an increase in the buffer pH. As an anionic polymer, Eudragit® L 30 D-55 is insoluble at low pH values and starts to dissolve at pH 5.5. The dissolution pH threshold of 5.5 for this polymer was confirmed by the result present in Figure 3.11; however, it is apparent that the polymer dissolution velocity of Eudragit® L 30 D-55 was very slow at this threshold pH.

Eudragit® L 30 D-55 polymer dissolved at higher rates from the double-coated glass beads than from the control-coated glass beads at all of the test pH values from 4.0 to 6.2. In addition, it is of note that Eudragit® L 30 D-55 started to dissolve from the double-coated glass beads at pH 4.0 compared to pH 5.5 from the control-coated beads. At pH 5.5, in contrast to the very slow dissolution speed from the control-coated beads, Eudragit® L 30 D-55 dissolved much faster from the double-coated glass beads, with the dissolution velocities of 5.7 and 0.4 %/min for the double coating and the control coating respectively.
Figure 3.12. Comparison of polymer dissolution velocities from the double-coated and the control-coated glass beads at different buffer pH, after 2 hours pre-treatment in pH 1.2 HCl.

It is also to be noted that the curve of polymer dissolution velocities by pH for the double coating has two slopes divided at pH 5.5; above pH 5.5, increasing the buffer pH, the velocities increased at a faster rate than below pH 5.5. It was observed during the test that the Eudragit® L 30 D-55 outer coat dissolved in different patterns at buffer pH above and below 5.5. At pH 5.5 and above, both the inner and the outer coat dissolved at the same time and contributed to the increase of RI-signals. At pH values below 5.5, the outer coat of the double-coated glass beads did not dissolve. However, during the dissolution process, the inner coat swelled, resulting in the rupture of the outer coat which allows the neutralized inner coat to dissolve and release into buffer, and thus contribute to the change of RI-signals. At the end of dissolution process, the inner coat completely dissolved and the outer coat floated...
away from the glass beads. This could explain the release of active ingredients from the double-coated enteric dosage forms at these low pH values.

The above polymer dissolution velocity results in different buffer pH were obtained after 2 hours acid pre-treatment. The double coating maintained the fast dissolution properties compared to the control coating after exposure to acid medium. However, it would be of interest to understand the influence of acid treatment on the dissolution rates of both the double coating and the control coating. Therefore, the polymer dissolution velocities of the double-coated and the control-coated glass beads with and without acid treatment were further compared at pH 5.5 (Figure 3.13).

![Figure 3.13. Comparison of polymer dissolution velocities from the double-coated and the control-coated glass beads at pH 5.5 with and without acid pre-treatment.](image)

Without the acid treatment, the dissolution speeds in buffer for both the control coating and the double coating were faster than after acid treatment. Although
Eudragit® L 30 D-55 does not dissolve in pH 1.2 HCl, upon exposure to acid, the hydrochloric acid can ingress into the film coat. The absorbed acid medium can thus delay the neutralization of the polymer by the alkaline buffer media in subsequent buffer testing, and therefore retard the polymer dissolution processes. Delayed drug release after acid treatment was also reported by Ibekwe et al. (2006a) for Eudragit® S and Eudragit® FS coating. Since Eudragit® L 30 D-55 polymer dissolution as well as the neutralization by buffer was relatively slow at pH 5.5, the influence of acid treatment on dissolution rate was highlighted at this pH value.

Interestingly, the influence of acid treatment on the dissolution of the double coating was less than the control coating, with 30 and 50% reduction after acid treatment respectively. This is likely because the acceleration of the dissolution speed of the double coating by the presence of the inner coat could compensate the retardation caused by the imbibed acid medium.

Although the commonly used *in vitro* acid-resistance testing requires 2 hours acid pre-treatment for enteric-coated products, *in vivo* the exposure time of the products to the acidic environment of the stomach may vary. In fasted stage, gastric emptying normally takes place from 0.5 to 2 hours (Park et al., 1984; Davis et al., 1986c; Marvola et al., 1987). The dissolution of the enteric coating as well as the consequent disintegration of the coated dosage form may be faster in cases where rapid gastric emptying takes place. This also highlighted the complex nature of the *in vivo* conditions which dosage forms may encounter, and the difficulty for using the standardized *in vitro* testing to predict the *in vivo* performance.

### 3.9.2 Correlation of polymer dissolution velocities to drug release results

Polymer dissolution velocities from the control-coated and the double-coated glass beads correlated well with drug release results obtained from the coated prednisolone tablets. No drug release from the control-coated tablets at pH values...
lower than 5.5 was explained by the extremely low polymer dissolution velocities from this formulation below pH 5.5. Drug release from the control-coated tablets was very slow in pH 5.5 and 5.6 buffer and became much faster in pH 5.8 buffer, which was also reflected by the polymer dissolution velocities at these buffer pH. Polymer dissolution speeds were low at pH 5.5 and 5.6, but substantially faster at pH 5.8. In general, polymer dissolution velocity increased with increasing buffer pH, resulting in faster drug release from the control-coated tablets.

The higher polymer dissolution rates from the double coating were also an explanation for the faster drug release from the double-coated tablets compared to the control-coated tablets. This correlation was better represented at buffer pH values below 5.8. Below pH 5.8, the polymer dissolution from the control coating was slow, so was the drug release from coated tablets. Therefore, the accelerated polymer dissolution rate by the double coating resulted in the increased drug release rate from the double-coated tablets. However, above pH 5.8, the polymer dissolution from the control coating was already high. Although it was also increased by the double coating, this increase was not able to be differentiated by drug release testing.

Another distinct characteristic of drug release profiles from the double-coated tablets was the substantial amount of drug released at pH values lower than 5.5. This is not because of the outer coat dissolution at these low pH values, nor the reduction of the dissolution pH threshold of the polymer. As explained by the polymer dissolution velocity test results, the outer coat Eudragit® L 30 D-55 was still not soluble at these low pH values, yet the swelling of the inner coat and the resultant rupture of the outer coat allowed the release of active ingredients.
SECTION 3: COATING DISSOLUTION PROCESS USING CONFOCAL LASER SCANNING MICROSCOPY

3.10 INTRODUCTION

As established by polymer dissolution velocity and drug release tests, the double-coated formulation accelerates the coat dissolution and drug release compared to the control coating in buffer. To better understand the mechanisms involved in the coat dissolution, it is desirable to visualize the actual coat dissolution processes of this double coating system and compare to the control coating. By adding fluorescent dyes into the coat, confocal laser scanning microscopy (CLSM) is a potential technique to provide this visualization of coat dissolution.

CLSM has been extensively used in cell biology and recently applied to characterize pharmaceutical dosage forms (Lamprecht et al., 2000a; Lamprecht et al., 2000b; Lamprecht et al., 2003; Wolf et al., 2005). The applications of CLSM in the pharmaceutical field are mainly focused on the investigation of the structure, composition and polymer distribution of microparticles and microcapsules. However, recent work has demonstrated that CLSM can also be used to characterize the film coating properties, such as the coating defects in the film-core interface and surface of coated tablets, drug diffusion from core to aqueous enteric film coat during coating process (Guo et al., 2002a), and drug permeability and release from enteric-coated pellets (Guo et al., 2002b). It was also used to investigate the drug release mechanisms within controlled-release dosage forms (Cutts et al., 1996). The critical early stages of gel layer formation and liquid ingress in hypromellose matrices can be visualized using confocal imaging (Melia et al., 1997; Gurjit et al., 2006).
The advantages of CLSM over conventional light microscopy are that it is able to produce high resolution images and eliminate the out of focus fluorescent light. Furthermore, CLSM is a non-invasive technique which could produce 3-D images of both the surface and the internal structure of the samples. The theoretical principle of CLSM is demonstrated in Figure 3.14. Excitatory laser light emitted by the laser system passes through a pinhole aperture and is reflected by a dichromatic mirror and scanned across the sample in a defined focal plane. Fluorescent light from the sample is collected by the objective and passes back through the dichromatic mirror and is focused on to a photomultiplier. The out of focus light which is emitted at sample points above and blow focal plane is rejected by a second pinhole placed in front of the photomultiplier. Therefore, only the in focus light is able to contribute to the resultant confocal images.

Figure 3.14. Demonstration of optical geometry of CLSM (adapted from Olympus, Fluoview resource center).
In addition to reveal the coat dissolution process of the double coating system and help to understand the mechanisms involved in the coating dissolution, it was also the aim of this study to examine the potential of CLSM as a tool for visualizing the coating dissolution processes of polymeric film coatings. Two fluorescent probes fluorescein and rhodamine B were chosen as markers added in the outer/control and the inner coat respectively. CLSM allows the simultaneous detection and unambiguous identification of these two markers by using different channels. Therefore, the coat dissolution processes of both the inner and the outer coat could be revealed simultaneously. Since it is not feasible to apply CLSM on large units such as tablets, coated prednisolone pellets were used for these tests. The coat dissolution processes were also correlated to the drug release profiles from coated pellets.

### 3.11 MATERIALS

Prednisolone was purchased from Aventis Pharma., Antony, France. Lactose (Pharmatose, 110μm) was purchased from Ellis & Everard, Essex, UK. Microcrystalline cellulose (Avicel® PH101) was obtained from FMC Corporation, Philadelphia, USA. Eudragit® L 30 D-55 was donated by Röhm GmbH, Darmstadt, Germany. Triethyl citrate (TEC) was purchased from Lancaster Synthesis, Lancashire, UK. Talc (fine powder) was purchased from VWR International Ltd, Poole, UK. All other reagents were purchased from Sigma, St. Louis, MO, USA. De-ionized water was used.
3.12 METHODS

3.12.1 Preparation of prednisolone pellets

Prednisolone pellets (0.71-1.0 mm) were prepared by extrusion and spheronization. Each pellet contains 35% prednisolone, 40% lactose and 25% microcrystalline cellulose (Avicel® PH101). Prednisolone was dry mixed with lactose and MCC for 15 minutes in a planetary mixer (model A707A, Kenwood, Hampshire, UK). Sufficient water was added and mixing continued at the same speed for a further 10 minutes in order to achieve a wet powder mass suitable for extrusion. A ram extruder system was used with a barrel of 2.54 cm internal diameter and 20.3 cm length to which was fitted a die of 1 mm diameter and 4 mm length. After the wet powder was packed into the barrel, a piston was inserted into the barrel to partially consolidate the wet mass. The barrel, die and piston assembly was then positioned under the crosshead of a mechanical testing instrument (model MX 50, J.J. Lloyd, Southampton, UK) and driven down at a constant rate of 200 mm/minute.

The products of the extrusion process were collected and processed using a 20.3 cm diameter spheronizer (GB Caleva Ltd., Sturminster Newton, UK), with a radial plate rotating at 1000 rpm for 15 minutes. The pellets formed from the spheronization were dried in a 60 °C oven for 24 hours and then sieved to get desired size range.

3.12.2 Coating of prednisolone pellets with Eudragit® L 30 D-55 formulations

3.12.2.1 Preparation of coating dispersions or solutions

Two formulations were used for coating prednisolone pellets:

Control coating: Eudragit® L 30 D-55 single coating, 5mg/cm²;
Double coating: inner coat – Eudragit® L 30 D-55 neutralized to pH 5.6 in the presence of 15% adipic acid, 5mg/cm²; outer coat – Eudragit® L 30 D-55, 5mg/cm².

Coating dispersions for the control and the double coating were prepared using the methods described in Section 3.4.2.1. Two percent rhodamine B (based on dry polymer weight) and 1% fluorescein (based on dry polymer weight) was dissolved into the inner coat and the outer/control coat formulation respectively. For each formulation, two batches of pellets were coated, one with fluorescent probes and one without.

3.12.2 Film coating for prednisolone pellets

The pellets (30 g for each batch) were coated using Strea-1 bottom spray fluidized bed spray coater (Aeromatic AG, Bubendorf, Switzerland). The coating conditions for each formulation are shown in Table 3.4.

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Inlet temperature (°C)</th>
<th>Outlet temperature (°C)</th>
<th>Capacity of fan (°C)</th>
<th>Atomizing pressure (bar)</th>
<th>Flow rate (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organic acid-containing</td>
<td>40</td>
<td>30</td>
<td>15</td>
<td>0.6</td>
<td>1.5</td>
</tr>
<tr>
<td>inner coat</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control and outer coat</td>
<td>40</td>
<td>30</td>
<td>15</td>
<td>0.6</td>
<td>2</td>
</tr>
</tbody>
</table>

The percentage total weight gain by the pellets was calculated using the same method described in Section 3.4.2.2. The surface area of pellets was calculated using the following formula:
The total weight of 100 pellets was measured and the average was used as the weight of one pellet. Since the size range of pellets was 0.71-1.0 mm, the medial diameter (0.855 mm) was used for calculating the surface area.

Coating process was continued until the required total weight gain was achieved. After each coating run, pellets were fluidized for a further 15 minutes to allow the coat to dry.

3.12.3 *In vitro* drug release testing for coated prednisolone pellets

Coated prednisolone pellets (150 – 200 mg) without fluorescent probes in the coat were used for drug release testing in pH 5.5 phosphate buffer using the method described in Section 3.4.4. The pH 5.5 phosphate buffer was prepared using the formula shown in Section 3.4.4.

3.12.4 Confocal Laser Scanning Microscopy testing

3.12.4.1 Dissolution of coated pellets for confocal testing

Dissolution of coated pellets for confocal testing was carried out in dark room using BP Method II paddle apparatus (Model 85T-M, G. B. Caleva Ltd., Dorset, UK). To prevent the agglomeration of pellets during dissolution testing, a net device (round, diameter 8 cm) with 20 chambers (round, diameter 1 cm) having a 250 μm supporting mesh at the bottom was designed and used (Figure 3.15). Twenty pellets, one in each chamber, were placed into the net device and put into the bottom of the
dissolution vessel with 900 ml of pH 5.5 phosphate buffer maintained at 37 ± 0.5 °C. Pellets were removed from the media at predetermined time points. The pH 5.5 phosphate buffer was prepared using the method described in Section 3.4.4.

Figure 3.15. The net device used for pellet dissolution testing.

3.12.4.2 Confocal testing

Pellets after the dissolution test were dried in room temperature and cut in half and examined under confocal laser scanning microscopy. A Zeiss LSM 510 META Laser Scanning Confocal Microscope (Zeiss, Germany), equipped with a Plan-Neofluer 5 x/0.15 air lens was applied. An Argon laser with 488 nm line and a Helium-Neon laser with 543 nm line were used. Images were stored as 1024×1024 pixel boxes (12-bit resolution). The resultant images were coloured with red (rhodamine B) and green (fluorescein) as a function of the emission wavelength for each of the probes.
3.13 RESULTS AND DISCUSSION

The coat dissolution processes for the control-coated and the double-coated pellets were visualized using CLSM. Acid-resistant properties of the coat were demonstrated by testing pellets before and after 2 hours treatment in pH 1.2 HCl (Figure 3.16). Both the control-coated and the double-coated prednisolone pellets exhibited good acid-resistance by showing no difference in the coats before and after acid treatment.

**Before acid treatment**

(A) The control-coated pellet  
(B) The double-coated pellet

**After 2 hours in acid**

(C) The control-coated pellet  
(D) The double-coated pellet

*Figure 3.16. Confocal images of the double-coated and the control-coated pellets before and after 2 hours treatment in pH 1.2 HCl*
The coat dissolution processes in pH 5.5 phosphate buffer are shown in Figures 3.17 and 3.18 for the control-coated and the double-coated pellets respectively. The buffer pH value was chosen as 5.5 to provide relatively slow coat dissolution and allow the sufficient number of sample points. At this buffer pH, the control coating dissolved gradually from the pellet core. Confocal image shows that after 70 minutes, the Eudragit® L 30 D-55 coat still remained intact. Starting from 80 minutes, the coat dissolved slowly and gradually. The rupture of the coat can be seen at 110 minutes, and after 140 minutes the coat completely dissolved.

\[\text{(A) 70 minutes in buffer} \quad \text{(B) 80 minutes in buffer} \quad \text{(C) 100 minutes in buffer} \]
\[\text{(D) 110 minutes in buffer} \quad \text{(E) 120 minutes in buffer} \quad \text{(F) 140 minutes in buffer} \]

**Figure 3.17.** Confocal images of the control-coated pellets at different time points in pH 5.5 phosphate buffer
In contrast to the slow dissolution process of the control coating, the double coating dissolved at an earlier time point and at a faster rate. Both the inner and the outer coat remained intact after 30 minutes in pH 5.5 buffer. However, after 35 minutes, holes were seen in the inner coat of the double coating, while the outer coat still remained intact. As discussed in Section 2 of this chapter, Eudragit® L 30 D-55 dissolved very slowly in pH 5.5 buffer; however, buffer solution could penetrate through the outer coat and make contact with the inner coat. The inner Eudragit® L 30 D-55 polymer has been converted to a water soluble polymer by the neutralization using 1 M NaOH, and thus dissolved very fast upon contact with the buffer solution.

The fast dissolution of the inner layer accelerated the dissolving process of the outer Eudragit® L 30 D-55 coat. The outer coat dissolved together with the inner coat shortly after the dissolution of the inner coat. This is different from what was observed during polymer dissolution velocity tests at pH values lower than 5.5, where the outer coat did not dissolve but ruptured by the swelling of the inner coat. It is apparent from the confocal images that at pH 5.5, the swelling of the inner layer was not responsible for the rupture of the outer coat. The fast dissolution of the double coating system was the result of the accelerated dissolution rate of the outer coat due to the assistance of the dissolved inner coat. This is supported by the polymer dissolution velocity test results at pH 5.5 and above, that both the inner coat and the outer coat dissolved and contributed to the polymer dissolution rate.

The outer coat of the double coating dissolved and ruptured after 40 minutes in pH 5.5 buffer. Once dissolution had started, the dissolving speed of the outer coat was very fast; within 15 minutes, (after 55 minutes in pH 5.5 buffer), both the inner and the outer coat dissolved completely from the pellet core.
Figure 3.18. Confocal images of the double-coated pellets at different time points in pH 5.5 phosphate buffer

CLSM has proved to be a useful technique to probe the potential mechanisms and processes involved in the dissolution of the double-coated system. The fast dissolution of the neutralized inner coat before the outer coat was clearly shown. In addition, instead of the swelling of the inner coat rupturing the outer coat, the dissolution of the outer coat was accelerated by the assistance of the dissolved inner coat. The revelation of this distinct dissolution process of the double-coated system shed light on the understanding of the mechanisms involved in the double coating
dissolution. After the inflow medium has dissolved the inner coat, the methacrylic acid groups of Eudragit® L 30 D-55 which partially formed sodium salts by the neutralization can generate a buffer system in the inner layer. Furthermore, organic acid in the formulation was also partially neutralized and sodium salt of the acid was formed, which can further contribute to the above buffer system. In addition, the presence of the organic acid and its salt can increase the ionic strength of the inner layer.

This increased ionic strength and buffer capacity in the inner coat was believed to be associated with the accelerated dissolution rate of the outer coat. It has been found that increasing ionic strength and buffer capacity of dissolution media increases drug release rate from Eudragit® S coated tablets (Fadda and Basit, 2005). Spitael and Kinget (1977a) proposed that the dissolution rate of enteric polymers obeys Broensted catalysis law. The acid polymers (R-COOH) dissolve through the dissociation of the acids by proton transfer to the Broensted base H₂O, resulting in the formation of the conjugated base of the polymer and hydronium ions. In the presence of a basic salt, the rate of proton transfer is increased by the higher affinity of water in accepting a proton. It is possible that during the coat dissolution process, ions from the inner coat can migrate into the outer coat and thus assist the dissolution of the outer Eudragit® L 30 D-55 coat.

Another possible reason for the fast dissolution of the outer coat is the increased osmotic pressure in the inner coat due to the presence of sodium salts of the organic acid. The high osmotic pressure of the inner coat can drive more inflow medium into the coating system and thus assist the dissolution of the outer coat. The mechanisms of the double coating dissolution will be further investigated and discussed in the following chapter.

Drug release profiles from the control-coated and the double-coated prednisolone pellets was determined to correlate with the coating dissolution processes revealed
by CLSM. There was no drug release from the control-coated or the double-coated pellets in pH 1.2 HCl for 2 hours. In subsequent pH 5.5 buffer, the lag times of drug release were 40 and 105 minutes for the double-coated and the control-coated pellets, respectively (Figure 3.19). These lag time values correlate well with the outer coat rupture times obtained from CLSM. The drug release rate from the double-coated pellets was accelerated compared to the control-coated pellets, which could be explained by the fast coat dissolution speeds of both the inner and the outer coat of the double coating.

![Drug release profiles](image)

**Figure 3.19.** Drug release profiles of the Eudragit® L 30 D-55 double-coated and the control-coated prednisolone pellets in pH 5.5 phosphate buffer after pre-treatment in pH 1.2 HCl for 2 hours; and pellet cores in pH 5.5 phosphate buffer.
SECTION 4: OPTIMIZATION OF THE DOUBLE COATING SYSTEM

3.14 INTRODUCTION

The fast dissolution of the double-coated formulations has been established by drug release and polymer dissolution velocity testing. The mechanism of this fast dissolution was postulated as the accelerated dissolution rate of the outer coat due to the increased ionic strength, buffer capacity and osmotic pressure of the inner coat. Thus, it was the aim of this section of the study to optimize the double coating formulation to achieve faster dissolution rate than the investigated formulations. The influence of formulation factors in terms of the species and concentrations of organic acids in the inner coat, the neutralization value of the inner coat and the outer coat thickness on drug release from the double-coated tablets was exploited.

It has been highlighted in Chapter 1 that in vivo lag time before the disintegration of enteric-coated dosage forms is significantly longer than that is predicted by the in vitro dissolution tests. This is due to the inadequacy of the in vitro dissolution media to resemble the luminal fluid of the small intestine. Not only was the pH too high to represent the pH conditions of the proximal small intestine, the volume, viscosity, ionic composition and buffer capacity of the conventional pH 6.8 phosphate buffer employed in the in vitro dissolution tests are dissimilar from small intestine luminal fluids (Fallingborg et al., 1989; Dressman et al., 1990; Lindahl et al., 1997; Schiller et al., 2005).

Several attempts were reported in the literature to simulate small intestinal conditions, including the use of physiological bicarbonate buffer, biorelevant dissolution media and the application of dynamic artificial gastrointestinal systems.
However, all of the above approaches involve the prolonged preparation process and the high direct costs, which limit their extent of use as a routine method to screening coating formulations. In the present study, phosphate buffer with a pH value of 5.6 was used to discriminate the dissolution behaviour of different enteric coating formulations. This could simplify the dissolution method with easy preparation and low costs for routine use. The low pH value applied could also compensate the influence of other factors such as ionic strength, buffer capacity and volume of the dissolution media, and therefore, to better resemble small intestinal conditions and differentiate different enteric coating formulations.

The dissolution of the optimized double coating formulation was further tested in physiological bicarbonate buffer. Among factors which influence drug release from coating formulations, the constituent buffer salts, ionic strength and buffer capacity of the dissolution media have been well reported playing important roles on drug release from Eudragit® polymer coated dosage forms (Chan et al., 2001; Fadda and Basit, 2005; Ibekwe et al., 2006a). The main dissimilarity of the ionic composition between the conventional phosphate buffer media from the luminal fluids is that, the luminal fluids are buffered by bicarbonate and the phosphate levels are very low. Therefore, the use of physiological bicarbonate buffer as dissolution medium could add more confidence on the in vitro drug release data for predicting the in vivo performance of coated dosage forms.

A physiological salt solution (Hanks buffer) comprising various electrolytes including bicarbonate has been applied to investigate the in vitro dissolution performance of Eudragit® S and Eudragit® FS coated tablets (Fadda and Basit, 2005; Ibekwe et al., 2006a). Dissolution in this physiological buffer was found to be significantly slower compared to the conventional phosphate buffer and give better correlation to the in vivo disintegration results (Ibekwe et al., 2006b). However, Hanks buffer is only stable at pH 7.4 which is suitable for testing colonic delivery dosage forms, but too high for enteric-coated dosage forms aiming to target drugs to
the proximal small intestine. Another buffer agent 2-(N-morpholino)ethanesulfonic acid (MES buffer) was added into Hanks buffer to reduce the buffer pH to 6.8 which is the pH value normally employed for the \textit{in vitro} tests for enteric-coated formulations.

3.15 MATERIALS

Prednisolone was purchased from Aventis Pharma., Antony, France. Lactose (Pharmatose, 110µm) was purchased from Ellis & Everard, Essex, UK. Sodium carboxymethylcellulose (Ac-di-sol) was donated by FMC International, Cork, Eire. Polyvinylpyrrolidone (PVP) was purchased from VWR International Ltd, Poole, UK. Eudragit® L 30 D-55 was donated by Röhm GmbH, Darmstadt, Germany. Triethyl citrate (TEC) was purchased from Lancaster Synthesis, Lancashire, UK. Talc (fine powder) was purchased from VWR International Ltd, Poole, UK. All the salts used to prepare the buffers and 5 M HCl were of analytical grade and obtained from VWR International Ltd, Poole, UK. All other reagents were purchased from Sigma, St. Louis, MO, USA. De-ionized water was used.

3.16 METHODS

3.16.1 Coating of prednisolone tablets

In this section of the study prednisolone tablets (prepared using the methods described in Section 3.4.1) were double-coated with different Eudragit® L 30 D-55 formulations, in terms of organic acid species and concentrations in the inner coat, neutralization value of the inner coat and outer coat thickness. Table 3.5 summarizes the variables of the double coating formulations. The concentrations of the organic
acid were based on the dry weight of the polymer. Prednisolone tablets were also coated with the control coating with polymer amount of 3, 4 and 5 mg/cm².

\textit{Table 3.5. Double coating formulations for prednisolone tablets}

<table>
<thead>
<tr>
<th>Concentration of organic acids in the inner coat</th>
<th>pH of inner coating solutions</th>
<th>Outer coat polymer quantity (mg/cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10% pH 5.6</td>
<td></td>
<td>3, 4 and 5</td>
</tr>
<tr>
<td>Adipic acid 15% pH 5.6</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>10% pH 5.6, 5.8 and 6.0</td>
<td></td>
<td>3, 4 and 5</td>
</tr>
<tr>
<td>Citric acid 15% pH 5.6</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>20% pH 5.6</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>30% pH 5.6</td>
<td></td>
<td>5</td>
</tr>
</tbody>
</table>

The preparation of the Eudragit® L 30 D-55 control coating and the outer coat of the double coating followed the same method described in Section 3.4.2.1. To prepare the inner coating dispersions, adipic acid and citric acid with the concentrations described in Table 3.5, and 5% triethyl citrate (TEC) (based on polymer weight) were dissolved in water, and added into Eudragit® L 30 D-55 dispersions. The above dispersions were then neutralized to the pH values specified in Table 3.5 for different formulations using 1 M NaOH and the dispersions all turned to clear solutions. Fifty percent talc (based on polymer weight) was homogenized in water.
and added to these solutions. The amount of water in the formulation was calculated to obtain a 10% total solid content of the coating dispersion.

The tablets (40g for each batch) were coated using Strea-1 bottom spray fluidized bed spray coater (Aeromatic AG, Bubendorf, Switzerland). The coating conditions and the calculation of percentage total weight gain based on the polymer quantity required for each formulation are the same as in Section 3.4.2.2. Coating process was continued until the required total weight gain was achieved. After each coating run, tablets were fluidized for a further 15 minutes to allow the coat to dry.

3.16.2 *In vitro* drug release testing

*In vitro* drug release testing followed the method described in Section 3.4.4. Tablets were placed for 2 hours into pH 1.2 HCl, and subsequently into sodium phosphate buffer (pH 5.6 and 6.8), pH 7.4 Hanks buffer and pH 6.8 Hanks/MES (2-(N-morpholino)ethanesulfonic acid) buffer. Sodium phosphate buffer (pH 5.6) was prepared using the formula described in Section 3.4.4 and 5 L pH 6.8 sodium phosphate buffer was prepared by mixing 2.4 L stock solution I and 2.6 L stock solution II (the formula of stock solutions were also reported in Section 3.4.4). Table 3.6 shows the formula for preparing pH 7.4 Hanks buffer (Fadda and Basit, 2005). All the other salts except NaHCO₃ and CaCl₂ were dissolved in 4.5 L water in a 5 L volumetric flask stirring with a magnetic stirrer. After all of the salts in the flask have been dissolved, NaHCO₃ was added into the solution and dissolved while the flask is closed. CaCl₂ was added and dissolved in the flask at the end to prevent precipitation. Water was added into the flask to make up to 5 L. Hanks/MES buffer (pH 6.8) was prepared by adding 5 ml 1 M MES solution into 5 L Hanks buffer. Hanks and Hanks/MES buffer were used immediately after preparation and no degasification was carried out.
Table 3.6. Formula for pH 7.4 Hanks buffer

<table>
<thead>
<tr>
<th>Salts</th>
<th>Concentration (mM/L)</th>
<th>Quantities for 5 L solution (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NaCl</td>
<td>136.9</td>
<td>40.01</td>
</tr>
<tr>
<td>KCl</td>
<td>5.37</td>
<td>2</td>
</tr>
<tr>
<td>MgSO₄·7H₂O</td>
<td>0.812</td>
<td>1</td>
</tr>
<tr>
<td>CaCl₂</td>
<td>1.26</td>
<td>0.7</td>
</tr>
<tr>
<td>Na₂HPO₄·2H₂O</td>
<td>0.337</td>
<td>0.3</td>
</tr>
<tr>
<td>KH₂PO₄</td>
<td>0.441</td>
<td>0.3</td>
</tr>
<tr>
<td>NaHCO₃</td>
<td>4.17</td>
<td>1.75</td>
</tr>
</tbody>
</table>

Buffer capacities of pH 6.8 sodium phosphate buffer and pH 6.8 Hanks/MES buffer were determined by adding 0.3 ml 0.1 M HCl to 100 ml buffer and measuring the pH change of the buffer (ΔpH). The buffer capacity (β) was calculated using equation 1 (Martin, 1993).

\[
\beta = \frac{\text{mmol} / L(\text{HCl})}{\Delta \text{pH}}
\]  

Eq. 1

3.16.3 Acid uptake by tablets

Ten coated prednisolone tablets were weighted and subjected to dissolution conditions for 2 hours in pH 1.2 HCl. After 2 hours the tablets were removed and excess medium drained and blotted with filter paper from around the tablet. The tablets were then weighed and acid uptake was calculated.
3.16.4 Scanning electron microscopy

Some of the tablets coated with the inner coat formulation were removed from the coating machine without over coating with the outer coat. The inner coat film surface of these tablets was examined by scanning electron microscopy (SEM), using a JEOL JSM-35 Scanning Microscope.

The coat thickness of the control-coated tablets was determined at the edge and the surface of the tablet using SEM. The test was conducted in triplicate.

3.16.5 Differential scanning calorimetry

The effect of adipic acid and citric acid in the inner coat of the double-coated formulations on the thermal properties of the film coat was determined using differential scanning calorimetry (DSC). Eudragit® L 30 D-55 dispersions were neutralized to pH 5.6 using 1 M NaOH and became clear solutions. Different concentrations of adipic acid and citric acid were dissolved into the above Eudragit® L 30 D-55 solutions. Films were cast from these solutions by pouring on Teflon dishes and dried at room temperature until they could be removed from the dish. The removed films were then continued to dry in an oven at 50 °C for 24 hours.

After drying, the films were stored in a desiccator over silica gel for 72 hours prior to analysis using DSC (Pyris 1, PerkinElmer Instruments, Bucks, UK). Approximately 10 mg of sample was weighed and sealed into an aluminum pan. The samples were heated at a rate of 100 °C/minute from -20 to 160 °C. The heating process was repeated and the second heating results were used for data analysis. Glass transition temperature (T_g) values of the samples were reported as the half change in specific heat capacity of the transition. The test was performed in triplicate.
3.17 RESULTS AND DISCUSSION

3.17.1 Influence of species and concentration of organic acid in the inner coat on drug release

Table 3.7 summarizes the drug release results (lag time and $T_{50\%}$ - the time for 50% drug release) of prednisolone tablets double-coated with formulations having different adipic acid and citric acid concentrations in the inner coat in pH 5.6 phosphate buffer following 2 hours exposure to pH 1.2 HCl. Increasing adipic acid concentration from 10% to 15%, drug release rate increased, whereas, further increasing to 20%, drug release rate decreased. In the case of citric acid, increasing the concentration from 10% to 30% has very little influence on drug release rate. When comparing the effects of different acid species, citric acid formulations showed faster drug release than adipic acid formulations.

<table>
<thead>
<tr>
<th></th>
<th>Adipic acid</th>
<th></th>
<th></th>
<th>Citric acid</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10%</td>
<td>15%</td>
<td>20%</td>
<td>10%</td>
<td>15%</td>
<td>20%</td>
</tr>
<tr>
<td><strong>Lag time</strong> (min ± SD)</td>
<td>42 ± 8</td>
<td>25 ± 5</td>
<td>33 ± 3</td>
<td>28 ± 8</td>
<td>25 ± 0</td>
<td>18 ± 8</td>
</tr>
<tr>
<td><strong>$T_{50%}$</strong> (minute ± SD)</td>
<td>90 ± 5</td>
<td>67 ± 3</td>
<td>110 ± 10</td>
<td>70 ± 9</td>
<td>62 ± 3</td>
<td>60 ± 5</td>
</tr>
</tbody>
</table>

SEM pictures show that 10% and 15% adipic acid inner coat formulation had smooth film surface, but the film surface became rough with 20% adipic acid (Figure 3.20).
Figure 3.20. Scanning electron micrographs of the surface of different inner coats of the double-coated prednisolone tablets.
After coating with 20% adipic acid inner coat, crystals were visible on the film coat surface, indicating that the Eudragit® L 30 D-55 film was not miscible with high adipic acid concentration. This incompatibility of the polymer film with high concentrations of adipic acid likely contributed to the decreased drug release rate from the double-coated tablets. Inner coats containing citric acid in general showed less smooth surface than adipic acid-containing formulations (Figure 3.20), indicating that citric acid has less plasticizing effect than adipic acid. The roughness of the film surface of the citric acid inner coat increased with increasing the citric acid concentration. When the citric acid concentration was above 20%, large crystals were seen on the film surface and the film coat became very brittle and easily broke in the fluid bed when applying the outer coat.

$T_g$ values of Eudragit® L 30 D-55 film neutralized to pH 5.6 with different adipic acid and citric acid concentrations showed that adipic acid is a better plasticizer for Eudragit® L 30 D-55 film than citric acid (Figure 3.21). The inclusion of 10% and 15% adipic acid decreased the $T_g$ of the film, however, 20% adipic acid in the film did not reduce its $T_g$, which is attributable to the incompatibility of high concentration of adipic acid to the film as seen by SEM image. The presence of citric acid in the film did not decrease its $T_g$, indicating citric acid had no plasticizing effect on Eudragit® L 30 D-55. Although the film $T_g$ did not increase by increasing the concentration of citric acid, high citric acid concentration showed less miscibility with the polymer film and crystallized in the film as shown by SEM pictures.
3.17.2 Influence of outer coat thickness on drug release

The recommended amount of polymer applied on enteric-coated tablets for Eudragit® L 30 D-55 to achieve gastric resistance is 4-6 mg/cm²; however, it has been reported that enteric properties could be obtained with polymer quantity less than or at 3 mg/cm² depending on the solubility and ionization characteristics of the drug (Plaizier-Vercammen et al., 1992a; Garcia-Arieta et al., 1996; Dangel et al., 2000a; Dangel et al., 2000b). Studies in the previous sections of this chapter demonstrated that the double-coated prednisolone tablets with an outer coat of 5mg/cm² polymer exhibited good gastric-resistant properties. To achieve fast tablet disintegration and drug release, it is desirable to reduce the thickness of the outer coat without compromising the gastric-resistance of the system.

Prednisolone tablets were coated with the control-coated and the double-coated formulations with different coat/outer coat polymer amount. The control-coated

Figure 3.21. \( T_g \) values of Eudragit® L 30 D-55 films (neutralized to pH 5.6) with different adipic acid and citric acid concentrations.
prednisolone tablets with 3, 4 and 5 mg/cm\(^2\) polymer were tested in pH 1.2 HCl for 2 hours and showed no drug release. In subsequent pH 5.6 phosphate buffer, drug release rate increased with reducing the coating level (Figure 3.22).

**Figure 3.22.** Drug release profiles of the control-coated prednisolone tablets with different coat thicknesses in pH 5.6 phosphate buffer after pre-treatment in pH 1.2 HCl for 2 hours.

Polymer dissolution velocity testing showed that Eudragit\(^\text{®}\) L 30 D-55 dissolved very slowly at pH 5.6. It was observed during drug release testing that the coat of the control-coated tablets with 5 mg/cm\(^2\) polymer did not completely dissolve after 6 hours testing in pH 5.6 buffer. However, it remained intact as a “balloon” inside of which was the dissolution medium. Drug release from tablets coated with this coating level is the result of drug diffusion through the film coat. The control-coated tablets with 3 and 4 mg/cm\(^2\) polymer showed irregular drug release profiles, with pulsatile releases between plateaus. This is likely due to the burst release caused by the rupture of the film coat followed by the drug diffusion through the film coat. For 3 and 4 mg/cm\(^2\) film coating, although the coat still did not completely dissolve, ruptures of the coat were seen after testing in pH 5.6 buffer. This was apparent
especially at the edge of the tablet which has thinner coat than the surface due to the ununiformity of film formation during coating process (55.8 ± 8.9 μm and 86.1 ± 5.9 μm of film coat was found at the edge and surface of the 5 mg/cm² control-coated tablets respectively). These ruptures of the coat could induce the burst drug release. For 4 mg/cm² polymer coated tablets, the ruptures did not cause complete failure of the coat; the flexible coat sealed the opening and reformed a diffusion layer for drug release. In the case of 3 mg/cm² polymer coated tablets, the ruptures caused the failure of the coat and allowed the drug to leach out completely in a short time. Since drug release was not caused by the dissolution but the rupture of the coat for 3 and 4 mg/cm² polymer coated tablets, the drug release results were highly variable.

Drug release from prednisolone tablets coated with the two double-coated formulations containing 10% citric acid and 10% adipic acid in the inner coat with 3, 4 and 5 mg/cm² outer coat were investigated. There was no drug release from either of these two double-coated formulations in pH 1.2 HCl for 2 hours. Unexpectedly, in subsequent pH 5.6 phosphate buffer, drug release rates were in the order of: 4 mg/cm² > 5 mg/cm² > 3 mg/cm² (Figures 3.23 and 3.24). Drug release was faster from the double-coated tablets with 4 mg/cm² outer coat than 5 mg/cm² outer coat. However, the double-coated tablets with an outer coat level of 3 mg/cm² showed the slowest drug release.

It was observed during dissolution testing that, after pre-treatment in pH 1.2 HCl for 2 hours, tablets with a polymer amount of 3mg/cm² became soft and swelled, indicating that hydrochloric acid imbibed into the tablet coat and the core. The influx acid medium could partially convert the salts in the inner coat to acids by ion exchange and thus cause the loss of acceleration properties of the inner coat on drug release. There was no drug release from the double-coated tablets with an outer coat of 3 mg/cm² in acid; however, the outer coat of this thickness was not able to protect the inner coat from the influx of acid medium. Therefore, the following drug release in subsequent buffer became slow and highly variable.
**Figure 3.23.** Drug release profiles of the Eudragit® L 30 D-55 double-coated prednisolone tablets (10% citric acid in the inner coat) with different outer coat thicknesses in pH 5.6 phosphate buffer after pre-treatment in pH 1.2 HCl for 2 hours.

**Figure 3.24.** Drug release profiles of the Eudragit® L 30 D-55 double-coated prednisolone tablets (10% adipic acid in the inner coat) with different outer coat thicknesses in pH 5.6 phosphate buffer after pre-treatment in pH 1.2 HCl for 2 hours.
To prove that it was the influence of the acid medium that caused the slow release from the double-coated tablets with an outer coat of 3 mg/cm², acid uptake testing was conducted for the coated tablets. Tables 3.8 and 3.9 show the acid uptake of the control-coated and the 10% adipic acid double-coated prednisolone tablets after exposure to pH 1.2 HCl for 2 hours. For the control-coated tablets, reducing the coat thickness, acid uptake slightly increased but even tablets coated with 3 mg/cm² polymer exhibited low acid uptake, indicating good gastric-resistance. In the case of the 10% adipic acid double-coated tablets, 5 mg/cm² and 4 mg/cm² polymer coated tablets showed low acid uptake, but the acid uptake dramatically increased after reducing the outer coat to 3 mg/cm². These acid uptake values correlate to and could explain the drug release results in subsequent buffer.

Table 3.8. Acid uptake of the control-coated prednisolone tablets

<table>
<thead>
<tr>
<th>Coat thickness (mg/cm²)</th>
<th>Original weight (10 tablets, g)</th>
<th>After 2 hours in acid (10 tablets, g)</th>
<th>Acid uptake (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>2.1338</td>
<td>2.2419</td>
<td>5.07</td>
</tr>
<tr>
<td>4</td>
<td>2.2092</td>
<td>2.2852</td>
<td>3.44</td>
</tr>
<tr>
<td>5</td>
<td>2.2559</td>
<td>2.3178</td>
<td>2.74</td>
</tr>
</tbody>
</table>

Table 3.9. Acid uptake of the 10% adipic acid double-coated prednisolone tablets

<table>
<thead>
<tr>
<th>Outer coat thickness (mg/cm²)</th>
<th>Original weight (10 tablets, g)</th>
<th>After 2 hours in acid (10 tablets, g)</th>
<th>Acid uptake (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>2.2865</td>
<td>2.9362</td>
<td>28.41</td>
</tr>
<tr>
<td>4</td>
<td>2.3663</td>
<td>2.4943</td>
<td>5.41</td>
</tr>
<tr>
<td>5</td>
<td>2.3813</td>
<td>2.4581</td>
<td>3.23</td>
</tr>
</tbody>
</table>
The above results demonstrated that the double coating with 4 and 5 mg/cm\(^2\) outer coat was sufficient to give good acid-resistance and maintain the fast dissolution in buffer. However, compared to the control coating which showed acid-resistance at 3 mg/cm\(^2\), the outer coat of the double-coated tablets at this coating level was not able to protect the functional properties of the inner coat. For both the control coating and the outer coat of the double coating, reducing the coating level increased acid medium influx. However, different from the control-coated tablets, after the inner coat of the double-coated tablets came into contact with higher amount of influx acid medium, the water soluble components in the inner coat dissolved and created an osmotic pressure difference between the inner coat and the external environment. This osmotic pressure gradient induced more acid influx and thus further diminished the protective efficiency of the coat. Guo et al. (2002b) reported that 40% drug released from cellulose acetate phthalate coated pellets with a freely water soluble model drug riboflavin sodium phosphate after one hour in pH 1.2 HCl. The authors speculated that drug release from these enteric-coated pellets was driven by osmotic pressure gradient generated by the dissolution of the drug in the influx acid medium.

Another possible explanation is that the water soluble components in the inner coat can dissolve and migrate into the outer coat during the aqueous coating process. The migration of water soluble drugs or excipients into aqueous film coat has been well documented in the literature (Dansereau et al., 1993; Kane et al., 1994; Crotts et al., 2001; Guo et al., 2002b; Bruce et al., 2003a). It has been reported that the inclusion of water soluble drugs or excipients in the film coat can induce drug-polymer/excipient-polymer interactions changing the intrinsic features of the film such as softening, glass transition, crystallinity and melting point (Okhamafe and York, 1989). Yang and Ghebre-Sellassie (1990) reported that the dissolution of a significant amount of drug in the coating formulation can reduce the surface tension of the coating liquid which is essential for the development of the capillary pressure needed for the deformation of the polymeric spheres, and thus, leading to the formation of a less continuous film coat.
The undesired presence of water soluble components in the film coat and the resultant interaction with the polymer and the incomplete film formation require higher amount of polymer to achieve the end-use properties of the coat. This explains the number of reports in the literature that aqueous enteric coating with a water soluble drug substrate needs higher amount polymer application or a seal coating to achieve gastric-resistance compared to that with a water insoluble drug substrate (Bianchini et al., 1991; Crotts et al., 2001; Guo et al., 2002b). Therefore, it is understandable that the polymer amount required for the outer coat of the double coating with an inner coat containing water soluble components is slightly higher than the control coating which contains prednisolone as a model drug having a relatively low water solubility (2.225 g/L) (Yalkowsky and He, 2003) in the tablet core.

The results also demonstrated that it is possible to achieve faster drug release from the double-coated system by reducing the outer coat thickness. This was proven by the faster drug release from the 4 mg/cm\(^2\) outer coat formulation than the 5 mg/cm\(^2\) outer coat formulation. In the following stages of the study, the double-coated formulations were still applied an outer coat of 5 mg/cm\(^2\), in order to compare with the control coating with the same coating level.

### 3.17.3 Influence of the neutralization value of the inner coat on drug release

The drug release rates from the double-coated prednisolone tablets were increased by increasing the neutralization value of the inner coat polymer solution. This is shown by drug release profiles of the double-coated prednisolone tablets with 10% citric acid in the inner coat in pH 5.6 phosphate buffer following 2 hours pre-testment in acid (Figure 3.25). When the pH of the inner coat solution was increased from pH 5.6 to 5.8, the increase in drug release rate was limited. However, as the inner coat solution was neutralized to pH 6.0, drug release rate was
significantly increased, with the lag times of 5 and 40 minutes for pH 6.0 and pH 5.6 inner coat formulations respectively.

Increasing the neutralization value of the inner coat, more salts formed for both Eudragit® L 30 D-55 polymer and organic acid, therefore, the ionic strength and osmotic pressure of the inner coat were possibly increased, which contributed to the fast drug release rate. However, the coating process became problematic after neutralizing the inner coat solution to pH 6.0, due to the high viscosity of the coating solution, which caused the agglomeration of the tablets during the coating process. High atomizing pressure and low flow rate have been applied for pH 6.0 inner coating solution to avoid the tablet agglomeration, which was impractical due to the low coating capacity and prolonged coating time. Therefore, no further increase of the neutralization value beyond pH 6.0 was investigated.

![Figure 3.25](image)

**Figure 3.25.** Drug release profiles of the Eudragit® L 30 D-55 double-coated prednisolone tablets (10% citric acid in the inner coat) with different inner coat pH values in pH 5.6 phosphate buffer after pre-treatment in pH 1.2 HCl for 2 hours.
As described above, the double-coated tablets with an inner coat containing 10% citric acid and neutralized to pH 6.0 exhibited very fast dissolution rate in pH 5.6 phosphate buffer after 2 hours acid treatment. To better predict the in vivo performance of this double-coated formulation, drug release was determined in physiological bicarbonate buffers: pH 7.4 Hanks buffer and pH 6.8 Hanks/MES (2-(N-morpholino)ethanesulfonic acid) buffer. Table 3.10 compares the ionic composition and buffer capacities of human jejunal fluid, physiological and phosphate buffers.

Table 3.10. Electrolyte composition of intestinal fluid, physiological and phosphate buffers (mmol/L) (Fadda and Basit, 2005)

<table>
<thead>
<tr>
<th>Electrolyte</th>
<th>Human jejunal fluid</th>
<th>Hanks buffer (pH 7.4)</th>
<th>Hanks/MES buffer (pH 6.8)</th>
<th>Phosphate buffer I*</th>
<th>Phosphate buffer II**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bicarbonate</td>
<td>8.2</td>
<td>4.2</td>
<td>4.2</td>
<td>Not present</td>
<td>Not present</td>
</tr>
<tr>
<td>Phosphate</td>
<td>-</td>
<td>0.8</td>
<td>0.8</td>
<td>50</td>
<td>67</td>
</tr>
<tr>
<td>Potassium</td>
<td>5.4</td>
<td>5.8</td>
<td>5.8</td>
<td>50</td>
<td>Not present</td>
</tr>
<tr>
<td>Sodium</td>
<td>142</td>
<td>142</td>
<td>142</td>
<td>39</td>
<td>102</td>
</tr>
<tr>
<td>Chloride</td>
<td>126</td>
<td>143</td>
<td>143</td>
<td>Not present</td>
<td>Not present</td>
</tr>
<tr>
<td>Calcium</td>
<td>0.5</td>
<td>1.3</td>
<td>1.3</td>
<td>Not present</td>
<td>Not present</td>
</tr>
<tr>
<td>Magnesium</td>
<td>-</td>
<td>0.8</td>
<td>0.8</td>
<td>Not present</td>
<td>Not present</td>
</tr>
<tr>
<td>MES</td>
<td>Not present</td>
<td>Not present</td>
<td>1</td>
<td>Not present</td>
<td>Not present</td>
</tr>
<tr>
<td>Buffer capacity</td>
<td>2.4</td>
<td>1</td>
<td>15</td>
<td>23</td>
<td>15</td>
</tr>
</tbody>
</table>

* Phosphate buffer I: Two phases phosphate buffer with sodium and potassium phosphate salts (0.05 M)

** Phosphate buffer II: Sodium phosphate buffer solution (0.067 M)
Figures 3.26-3.28 show the drug release profiles from the control-coated and the double-coated (10% citric acid in the inner coat) prednisolone tablets in pH 6.8 sodium phosphate buffer, pH 7.4 Hanks buffer and pH 6.8 Hanks/MES buffer, respectively. Although drug release from the control-coated prednisolone tablets was very fast in pH 6.8 sodium phosphate buffer (phosphate buffer II), with only 5 minutes lag time, drug releases were relatively slow in pH 6.8 Hanks/MES buffer and pH 7.4 Hanks buffer (with both lag times of 35 minutes). This relatively slow drug release from anionic polymer coated dosage forms in physiological bicarbonate buffer compared to phosphate buffer agrees with findings in the literature (Fadda and Basit, 2005).

The slow drug release of the control-coated tablets in pH 7.4 Hanks buffer is attributable to the low buffer capacity of this buffer compared to pH 6.8 sodium phosphate buffer. Although pH 6.8 Hanks/MES buffer has a relatively high buffer capacity, the buffer species is bicarbonate instead of phosphate compared to pH 6.8 phosphate buffer. Fadda and Basit (2005) has reported that aside from buffer capacity, the buffer species played an important role on the drug release performance. Polymer dissociation and dissolution is slower in bicarbonate buffer than in phosphate buffer due to the low pKₐ values of the buffer salt. Spitael and Kinget (1977a) also reported that the dissolution of enteric polymer is directly related to the pKₐ values of the salts in the dissolution media. This can explain the long lag time of drug release from the control-coated tablets in pH 6.8 Hanks/MES buffer.
Figure 3.26. Drug release profiles of the Eudragit® L 30 D-55 double-coated and the control-coated prednisolone tablets in pH 6.8 sodium phosphate buffer after pre-treatment in pH 1.2 HCl for 2 hours.

Figure 3.27. Drug release profiles of the Eudragit® L 30 D-55 double-coated and the control-coated prednisolone tablets in pH 7.4 Hanks buffer after pre-treatment in pH 1.2 HCl for 2 hours.
Figure 3.28. Drug release profiles of the Eudragit® L 30 D-55 double-coated and the control-coated prednisolone tablets in pH 6.8 Hanks/MES buffer after pre-treatment in pH 1.2 HCl for 2 hours.

In the case of the double-coated tablets with an inner coat containing 10% citric acid and a neutralization value of pH 6.0, drug release was very fast in both pH 6.8 Hanks/MES buffer and pH 7.4 Hanks buffer, with lag times of 10 and 5 minutes respectively. Considering that small intestine luminal fluids are buffered by bicarbonate, the fast drug release from the double-coated tablets in these physiological bicarbonate buffers have significant implications on the fast in vivo disintegration and drug release of the double-coated dosage forms.

3.18 CONCLUSION

The novel double-coated system is shown here to be gastric-resistant. The drug release rate from this double-coated system is substantially accelerated in pH values resembling proximal small intestine conditions, compared to the control coating.
Eudragit® L 30 D-55 polymer dissolved faster from the double-coated system than from the normal control coating. The accelerated dissolution rate of the outer coat due to the presence of salts in the inner coat is the main mechanism involved in the fast dissolution of the double-coated system.

Improvement of drug release from the double-coated system can be achieved by reducing the outer coat thickness, although consideration needs to be given for maintaining sufficient acid-resistance. By optimizing the inner coat organic acid species/concentrations and the neutralization value, the double-coated formulation can achieve fast dissolution in physiological bicarbonate buffer, which implicates rapid in vivo disintegration and drug release.
CHAPTER 4

UNDERSTANDING THE MECHANISMS INVOLVED IN THE DISSOLUTION OF THE DOUBLE COATING SYSTEM
4.1 INTRODUCTION

In the previous Chapter, the concept of the double-coated system has been demonstrated in the form of applying Eudragit® L 30 D-55 normal coat on an inner coat comprising the neutralized Eudragit® L 30 D-55 polymer and organic acid. The accelerated coat dissolution and drug release from the double-coated system compared to the conventional single coating (control coating) was established. The double-coated system was optimized and the drug release lag times were reduced to 5-10 minutes in upper small intestinal pH condition (phosphate buffer, pH 5.6) and in physiological bicarbonate buffer (pH 6.8 and 7.4). These short lag times should ensure the fast in vivo disintegration and drug release. It was then of interest to understand the mechanisms involved in the fast coat dissolution and drug release from the double-coated system.

In Chapter 3, the CLSM study has demonstrated that the fast drug release from the double-coated system is the result of accelerated dissolution rate of the outer Eudragit® L 30 D-55 coat. This is due to the assistance of the rapidly dissolving inner coat, after coming into contact with the imbibed buffer medium. The physiochemical properties of the inner coat which could possibly assist in the dissolution of the outer coat are therefore of focus. These properties include the composition, ionic strength, buffer capacity and osmotic pressure of the inner coat, as well as the possible migration of the ions from the inner to the outer coat during dissolution process. The interplay between these factors in the inner coat with the dissolution mechanisms of the double-coated system are investigated in this chapter in the following aspects:

- Comparison studies are conducted to establish the roles of different formulation factors of the inner coat on the dissolution of the double-coated system;
The influences of ionic strength and buffer capacity of the inner coat on the outer coat dissolution are illustrated using titration curves of different Eudragit® L 30 D-55 formulations;

- Scanning electron microscopy/energy dispersive X-ray spectroscopy (SEM/EDX) are used to investigate the migration of ions from the inner to the outer coat;

- The influence of inner coat osmotic pressure on the dissolution of the double-coated system was investigated by determining the drug release rates in dissolution media with different osmotic pressures.

4.2 MATERIALS

Prednisolone was purchased from Aventis Pharma., Antony, France. Placebo glass beads (spherical, 5mm diameter) was purchased from Peco Laborbedarf GmbH, Darmstadt, Germany. Lactose (Pharmatose, 110μm) was purchased from Ellis & Everard, Essex, UK. Sodium carboxymethylcellulose (Ac-di-sol) was donated by FMC International, Cork, Eire. Polyvinylpyrrolidone (PVP) was purchased from VWR International Ltd, Poole, UK. Microcrystalline cellulose (Avicel® PH101) was obtained from FMC Corporation, Philadelphia, USA. Eudragit® L 30 D-55 was donated by Röhm GmbH, Darmstadt, Germany. Triethyl citrate (TEC) was purchased from Lancaster Synthesis, Lancashire, UK. Talc (fine powder) was purchased from VWR International Ltd, Poole, UK. All other reagents were purchased from Sigma, St. Louis, MO, USA. De-ionized water was used.

Hypromellose (HPMC E5, METHOCEL™ E5) was donated by Colorcon Inc., Dartford, UK. METHOCEL™ E5 contains hypromellose 2910 (USP 27) with a methoxyl content of 28-30% and hydroxypropyl content of 7-12%. It is water soluble, with a viscosity of 2% aqueous solution of 2.4-3.6 cps.
4.3 METHODS

4.3.1 Comparison studies

4.3.1.1 Coating of prednisolone tablets

Prednisolone tablets (prepared using the methods described in Section 3.4.1) were double-coated with four Eudragit® L 30 D-55 formulations having different inner coats (the inner coat formulations are described following as F1-F4). The preparation of Eudragit® L 30 D-55 outer coat for all of these formulations followed the same method described in Section 3.4.2.1. The preparations of the inner coat formulations are described as follows:

**F1: Eudragit® L 30 D-55 inner coat with organic acid but without neutralization**

Twenty percent citric acid and 10% triethyl citrate (TEC) (both based on polymer weight) were dissolved in water, and added into Eudragit® L 30 D-55 dispersion. Fifty percent talc (based on polymer weight) was homogenized in water and added into above dispersion. The amount of water in the formulation was calculated to obtain a 10% total solid content of the coating dispersion.

**F2: Eudragit® L 30 D-55 inner coat with neutralization but without organic acid**

Two inner coat formulations were prepared, with the neutralization to different levels (pH 5.8 and 6.0). Five percent TEC (based on polymer weight) was dissolved in water, and added into Eudragit® L 30 D-55 dispersion. The above dispersion was then neutralized to pH 5.8/6.0 using 1 M NaOH, and the dispersion changed to a clear solution. Fifty percent talc (based on polymer weight) was homogenized in water and added to above solutions. The amount of water in the formulation was calculated to obtain a 10% total solid content of the coating dispersion.
**F3: HPMC sub-coat**

Ten percent (w/w) HPMC E5 aqueous solution was prepared by dissolving HPMC E5 in water.

**F4: HPMC sub-coat with 10% sodium citrate**

Ten percent sodium citrate (based on polymer weight) was dissolved in water. HPMC E5 was then dissolved into the above solution to give a 10% (w/w) aqueous solution.

Coating conditions for the outer coat formulation followed the parameters described in Section 3.4.2.2. Coating parameters for different inner coat formulations are listed in Table 4.1.

### Table 4.1. Coating conditions of different inner coat formulations

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Inlet air temperature (°C)</th>
<th>Outlet air temperature (°C)</th>
<th>Capacity of fan</th>
<th>Atomizing pressure (bar)</th>
<th>Flow rate (ml/minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>40</td>
<td>30</td>
<td>15</td>
<td>0.2</td>
<td>2.0</td>
</tr>
<tr>
<td>F2</td>
<td>40</td>
<td>30</td>
<td>15</td>
<td>0.2</td>
<td>0.5-1.0</td>
</tr>
<tr>
<td>F3</td>
<td>40</td>
<td>30</td>
<td>15</td>
<td>0.2</td>
<td>1.5</td>
</tr>
<tr>
<td>F4</td>
<td>40</td>
<td>30</td>
<td>15</td>
<td>0.2</td>
<td>1.5</td>
</tr>
</tbody>
</table>

The quantities of polymer applied on the outer coat and the inner coat of these formulations were the same: 5mg/cm², except for the inner coat of F3, on which 1, 3, and 5 mg/cm² of polymer were applied.
The tablets (40g for each batch) were coated using Strea-1 bottom spray fluidized bed spray coater (Aeromatic AG, Bubendorf, Switzerland). The calculation of percentage total weight gain based on the polymer quantity required for each formulation was the same as in Section 3.4.2.2. Coating process was continued until the required total weight gain was achieved. After each coating run, tablets were fluidized for a further 15 minutes to allow the coat to dry.

4.3.1.2 In vitro drug release testing

In vitro drug release testing followed the method described in Section 3.4.4. Tablets were placed for 2 hours into pH 1.2 HCl, and subsequently into pH 5.6 sodium phosphate buffer. Sodium phosphate buffer (pH 5.6) was prepared using the formula described in Section 3.4.4.

4.3.2 Influence of ionic strength and buffer capacity on the double coating dissolution

4.3.2.1 Ionic strength

The influence of ionic strength on the dissolution of Eudragit® L 30 D-55 was evaluated using titration method. The tested formulations included pure Eudragit® L 30 D-55 dispersion and Eudragit® L 30 D-55 dispersions containing salt or acids, including sodium citrate, citric, adipic and benzoic acid. The preparation of these formulations is described as follows:

Fifty grams of Eudragit® L 30 D-55 dispersion (30% solid content) was used for the titration. Fifteen percent of salt or acid (based on polymer weight) was dissolved in water and added into Eudragit® L 30 D-55 dispersion. The polymer concentration was adjusted to 10% w/w. In the case of dissolving adipic acid and benzoic acid, 1 M NaOH was added in water to help the dissolution. After adding the adipic acid
and benzoic acid solution into Eudragit® L 30 D-55 dispersion, the pH of the dispersion was adjusted to pH 4.5 using 1 M NaOH. The amount of 1 M NaOH consumed for dissolving the acids and adjusting the dispersion pH was recorded.

Titrations of Eudragit® L 30 D-55 dispersions were performed at 25 °C by drop wise addition of 1 M NaOH as the titrant, until a pH of 7.0 was achieved. A pH-meter (Hanna PH211, Hanna instruments, Leighton Buzzard, UK) equipped with a combination electrode and calibrated with standard buffer solutions (pH 4.00 ± 0.01 and pH 7.00 ± 0.01, at 25 °C) was used for the pH measurements. Solutions were agitated with a magnetic stirrer and a Teflon coated stirring bar.

4.3.2.2 Buffer capacity

Buffer capacities of citric acid and adipic acid solutions with the same concentration and neutralization value as in the corresponding inner coat formulations were determined. A fifteen percent (w/w) acid solution was prepared by dissolving the acid in water. Citric acid and adipic acid in the solution were neutralized to the same value as in the inner coat formulation by adding 1 M NaOH. Buffer capacity of the solutions was then measured following the method described in Section 3.16.2.

4.3.3 Migration of sodium ions from the inner to the outer coat of the double coating system

4.3.3.1 Preparation of samples

To demonstrate the migration of ions from the inner coat to the outer coat, sodium was chosen as a representative ion of salts and acids present in the inner coat. This is because in the original double-coat sodium ions were only present in the inner coat due to the neutralization of the inner coat using 1 M NaOH. The migration of sodium was investigated by determining its distribution throughout the inner and
the outer coat of the double-coated system during dissolution testing. Scanning electron microscopy/energy dispersive X-ray spectroscopy (SEM/EDX) was applied as the technique to determine this distribution. This ion migration study was conducted on coated pellets instead of tablets, because of the easier examination of pellets under microscopy than tablets.

Prednisolone pellets (prepared using the method described in Section 3.12.1) were double-coated with Eudragit® L 30 D-55 as the following formulation: inner coat – Eudragit® L 30 D-55 neutralized to pH 5.6 in the presence of 15% adipic acid, 5mg/cm²; outer coat – Eudragit® L 30 D-55, 5mg/cm². The preparation of the coating formulation and coating conditions were described in Section 3.4.2.1. The amount of polymer applied on the inner and the outer coat of the double coating was the same: 5mg/cm². The double-coated pellets were brought into pH 5.5 sodium phosphate buffer using the net device described in Section 3.12.4.1. Pellet samples were collected at 5 minutes intervals until 55 minutes in buffer, and carefully dried in a 40 °C oven.

4.3.3.2 Determination of sodium distribution using scanning electron microscopy/energy dispersive X-ray spectroscopy (SEM/EDX)

The dried pellets were carefully cut in half and the cross-sections of the film coat were examined by SEM using a JEOL JSM-840A Scanning Microscope. Sodium distribution at the cross-section of the film coat of the double-coated pellets were examined using an EDX detector (model OXFORD INCA 200). The EDX detector equips with a Liquid Nitrogen cooled X-ray detector (Si(Li) - silicon with lithium) having 10 mm² crystal area. The working distance for the EDX detector was 15 mm ± 1 and the electron energy (acceleration voltage) was 15 keV. All the samples for EDX testing were coated with carbon (~ 30 -40 nm). EDX mapping was carried out by dividing the SEM picture of the cross-section of the film coat up into 512 x 384 points. Complete EDX spectra were produced (multiple and average) in every point.
and a spatial distribution of single element were extracted (using the INCA software).

To determine the sodium ion concentration in the inner and outer coat of the double-coated pellets, the SEM picture of the cross-section of the film coat was divided into 10 small square sections (Figure 4.1), and the mass percentage of sodium ions in each section was measured.

![Figure 4.1. SEM picture of the cross-section of the double-coated pellets and the division of the coat into sections.](image)

4.3.4 Influence of inner coat osmotic pressure on drug release from double-coated formulations

4.3.4.1 Determination of acid and buffer uptake of the double-coated system

To determine the osmotic pressure of the inner coat of the double-coated system after acid treatment, the amount of acid taken up by the inner coat were measured.
The buffer uptake of the double-coated formulation was used to demonstrate the extent of the absorption of buffer medium by the double-coat system before its dissolution. Coated glass beads were used to investigate the acid and buffer uptake, due to the elimination of the influence of the core material on the results.

Glass beads were coated with the control coating and a double coating formulation which contained an inner coat with 10% citric acid and neutralized to pH 5.6. The preparation of the coating formulation and coating conditions were described in Section 3.8.1. The amount of polymer applied on the control coating and the inner and outer coat of the double coating were the same: 5mg/cm².

Ten coated glass beads were weighted and subjected to dissolution conditions for 2 hours in pH 1.2 HCl. After 2 hours the beads were removed and excess medium were drained and blotted with filter paper from around the beads. The beads were weighed again. The beads after the acid treatment were then brought into pH 5.6 sodium phosphate buffer in dissolution conditions and removed from the buffer every 5 minutes. After the surfaces were carefully blotted, the beads were weighed and quickly put back into the buffer medium. The percentage weight change of the beads (acid and buffer uptake) was calculated.

4.3.4.2 Influence of osmotic pressure on drug release

In order to evaluate the effect of inner coat osmotic pressure on the dissolution of the double-coated tablets, drug release studies of the double-coated tablets were conducted in media of different osmotic pressures. To chose the media osmotic pressure and give an osmotic gradient between the media and the inner coat, the osmotic pressure of the inner coat after 2 hours acid treatment was calculated in the following steps:
(1) The concentration of salts and acids in the inner coat after acid treatment was
calculated based on the acid uptake of the inner coat;

(2) Acid and salt solutions of above concentrations were prepared and the osmotic
pressures of these solutions were measured;

(3) The inner coat osmotic pressure was calculated by summing the osmotic
pressure of the corresponding salt and acid in the inner coat formulation.

Urea was used as the osmotic agent to increase the osmotic pressure of the
dissolution media. The osmotic pressures of pH 5.6 sodium phosphate buffer
containing different concentrations of urea were also measured. The measurements
of osmotic pressure were carried out using an osmometer (Hermann Roebling
MESSTECHNIK, Berlin, Germany), with an upper limit of 1999 mOsm/kg H₂O.
The instrument was calibrated using 300 mOsm standard solution prior to use.

To prepare the dissolution media, different amounts of urea were added into pH 5.6
sodium phosphate buffer, and the pH of the buffer was adjusted to 5.6 ± 0.5. Release
studies were performed using the dissolution testing method described in Section
3.4.4.

4.4 RESULTS AND DISCUSSION

4.4.1 Comparison studies

To understand the dissolution mechanisms of the double-coated system, it would be
helpful to establish the roles of different formulation factors on drug release. These
factors include the neutralization, the presence of organic acid and the polymer type
in the inner coat. Eliminating or changing these factors from/in the formulation and
comparing the drug release profiles could allow the understanding of the influence
of these factors on drug release.
Drug release from the double-coated system which contains an inner coat with organic acid but without neutralization was investigated to elucidate the significance of neutralization on drug release. The same method was applied to prove the importance of the presence of organic acids in the inner coat, by comparing with the double-coated system with the inner coat neutralization but without organic acids.

In the double-coated system, Eudragit® L 30 D-55 polymer applied on the inner coat has been changed into a water soluble polymer by the neutralization. The question arises: is this inner coat polymer exchangeable with other water soluble polymers, such as low viscosity hypromellose (HPMC)? To answer this question, the inner coat of the double-coated system was changed to HPMC E5 with and without additional salts. Drug release from the HPMC sub-coated system was compared with the Eudragit® L 30 D-55 double-coated system.

4.4.1.1 Inner coat with organic acid but without neutralization

It has been postulated that the neutralization of the inner coat Eudragit® L 30 D-55 into a water soluble polymer is crucial for the fast drug release from the double-coated formulations. However, to illustrate the significance of the inner coat neutralization on drug release, it is of interest to demonstrate the drug release from the double-coated formulation containing organic acid in the inner coat but without neutralization.

Drug release from prednisolone tablets coated with a double coating formulation having 20% citric acid in the inner coat but without neutralization was determined. No drug release was shown in pH 1.2 HCl for 2 hours. In subsequent pH 5.6 phosphate buffer, there was no drug release from this double-coated prednisolone tablets for 12 hours (Figure 4.2).
Citric acid in the inner coat dissolved after coming into contact with the influx buffer medium. This could contribute to a decreased microenvironment pH, adjacent to the Eudragit® L 30 D-55 outer coat, thus resulting in the lack of drug release from this double-coated formulation. The effect of core pH on the disintegration time of enteric-coated tablets has been elucidated by Dressman and Amidon (1984). The in vivo disintegration times of enteric-coated tablets with a core pH value of three were considerably longer than tablets with a core pH of five. It has also been reported in the literature that, the microenvironment pH surrounding the Eudragit® L 30 D-55 enteric-coat decreased by the inclusion of citric acid in the tablet core or sub-coat (Crotts et al., 2001; Bruce et al., 2003b). The ionization and dissolution of the polymer in pH 6.8 phosphate buffer were consequently suppressed.

In the present study, since the test buffer medium has low pH value (pH 5.6), if the microenvironment pH decreased to lower than the dissolution pH threshold of the
Eudragit® L 30 D-55 polymer (pH 5.5), there would be no dissolution of the polymer. Therefore, no drug would release from the coated tablets. Furthermore, the non-neutralized inner coat had no acceleration to the outer coat dissolution, and it also contributed to a very thick total coat (10 mg/cm³). It is not difficult to imagine that, drug release from Eudragit® L 30 D-55 coat with such a thickness would be very slow in pH 5.6 phosphate buffer.

4.4.1.2 Inner coat with neutralization but without organic acid

To identify the effect of the presence of organic acid in the inner coat on drug release from the double-coated tablets, prednisolone tablets were coated with double coating formulations with inner coats neutralized to pH 5.8 and 6.0 respectively using 1 M NaOH, but without the presence of organic acid. With the absence of organic acid, Eudragit® L 30 D-55 dispersion has to be neutralized to a higher pH value (5.8) to completely dissolve the polymer, compared to the formulation with organic acid (pH 5.6). Drug release rates from these double-coated tablets with neutralized inner coat but without organic acid were accelerated, compared to the very slow drug release from the control-coated tablets in pH 5.6 phosphate buffer, after 2 hours in pH 1.2 HCl (Figure 4.3).

Even without the presence of organic acid, since Eudragit® L 30 D-55 polymer in the neutralized inner coat was applied as a solution, upon exposure to the imbibed buffer medium, it dissolved quickly. The methacrylic acid groups of Eudragit® L 30 D-55 in this neutralized inner coat partially formed sodium salts which, together with the rest of the acid groups, created a buffer system. In addition, the ionic strength of the inner coat was increased due to the presence of these sodium salts. This buffer system and the increased ionic strength in the inner coat could contribute to the accelerated drug release from this double-coated formulation compared to the control-coated formulation.
However, drug release rates from the double-coated tablets with neutralized inner coat but without organic acid were slower than from the double-coated tablets with inner coat having corresponding pH value but in the presence of 10% citric acid (Figure 4.3). This indicates that the addition of organic acid in the inner coat was critical to further increase the drug release rate. This is attributable to the further increase of the buffer capacity and ionic strength of the inner coat by the neutralization of the organic acids. Furthermore, as small molecular weight components, the sodium salts of the organic acid could create an osmotic pressure gradient between the inner coat and the external environment, which could drive more medium influx into the double-coated system, thus further accelerating the coat dissolution and drug release.
4.4.1.3 Comparison with hypromellose (HPMC) as sub-coat

**Drug release from HPMC sub-coated tablets**

The influence of inner coat polymer type on drug release rate from the double-coated system could be demonstrated by changing the partially neutralized Eudragit® L 30 D-55 inner coat to HPMC sub-coat. In addition, hydrophilic polymers such as HPMC and polyvinyl alcohol are commonly used as sub-coat materials for enteric-coated dosage forms. Acid-liable drugs, such as proton pump inhibitors, could degrade in enteric-coated dosage forms due to the interaction between the drug and acidic enteric polymer, during film coating process or in solid state during storage (Riedel and Leopold, 2005a; Riedel and Leopold, 2005b; Stroyer et al., 2006). Polymeric sub-coats are then applied between the core and the enteric coating to prevent such degradation.

Sub-coats were also used to improve the acid-resistant properties of enteric-coated dosage forms with a highly water soluble substrate (Guo et al., 2002b; Bruce et al., 2003a; Bruce et al., 2003b). The sub-coat could seal the water-soluble substrate to prevent the migration of active ingredient into the enteric coating, thus reducing the roughness of the resultant film. Moreover, upon exposure to acidic medium, the sub-coat hinders the inflow medium to contact and dissolve the water-soluble active. Therefore premature drug release in acid could be prevented.

The application of hydrophilic sub-coats could also influence drug release in buffer. It has been reported that the release of citric acid from enteric-coated tablets in pH 6.8 phosphate buffer was delayed by the decrease in pH at the coat-core interface, due to the dissolution of the citric acid (Crotts et al., 2001). A HPMC sub-coat inhibited the diffusion of dissolved citric acid into the enteric coat and thus prevented delayed release. However, little work has been done on the influence of polymeric sub-coats on the dissolution properties of enteric-coated dosage forms with a neutral substrate, especially in upper small intestinal pH conditions.
Therefore, the influence of HPMC sub-coating on drug release from prednisolone tablets at pH condition simulating the upper small intestine was investigated.

Drug release rates from tablets sub-coated with different amount of HPMC in pH 5.6 phosphate buffer after 2 hours in pH 1.2 HCl were shown in Figure 4.4, and compared with the control-coated tablets. Drug release rates were increased with the addition of HPMC layer underneath the Eudragit® L 30 D-55 coat compared with the control coating. It was sufficient to accelerate drug release with 1 mg/cm² of HPMC sub-coat. Increasing the HPMC amount in the sub-coat to 3 mg/cm², drug release rate increased; but further increasing the polymer amount to 5 mg/cm², drug release rate decreased.

Figure 4.4. Comparison of drug release profiles of the Eudragit® L 30 D-55 control-coated prednisolone tablets with the HPMC sub-coated tablets in pH 5.6 phosphate buffer after pre-treatment in pH 1.2 HCl for 2 hours.
Coat dissolution process of HPMC sub-coating

The possible explanation for the acceleration of drug release by HPMC sub-coat could be the hydrophilicity of the HPMC polymer. However, as demonstrated in Chapter 3 for the double-coated system, it would be of use to visualize the coat dissolution process of the HPMC sub-coated system. By comparing the dissolution processes, it could also lead to further understanding of the coat dissolution mechanisms of these two coating systems. The coat dissolution process of the 3 mg/cm² HPMC sub-coated formulation was demonstrated using Confocal Laser Scanning Microscopy (CLSM). As for the double-coated and the control-coated formulations described in Chapter 3, pellets were also used in this study, for visualizing the dissolution of the whole coat system. Figure 4.5 shows that the HPMC sub-coated pellets exhibited good acid-resistance.

![Image of Confocal images of HPMC sub-coated pellets before and after acid treatment](image-url)

**Figure 4.5.** Confocal images of the HPMC sub-coated pellets before and after 2 hours in pH 1.2 HCl

After 2 hours acid treatment, pellets were tested in subsequent pH 5.5 phosphate buffer, which was used for testing the double-coated and the control-coated pellets in Chapter 3. Figure 4.6 shows the coat dissolution process of the HPMC sub-coated pellets in pH 5.5 phosphate buffer. The outer coat of the HPMC sub-coated pellets did not change after 50 minutes in pH 5.5 phosphate buffer; however, holes were seen in the inner coat.
It has been discussed in Chapter 3 that, Eudragit® L 30 D-55 dissolved very slowly in pH 5.5 buffer. However, buffer solution could penetrate through the outer coat and contact with the HPMC inner coat. The hydrophilic polymer HPMC dissolved very fast upon exposure to the imbibed buffer solution and led to the formation of gel. Increasing the exposure time to buffer, the gel of the inner HPMC layer absorbed more buffer solution and swelled. This swelling of the inner layer led to the distortion of the outer coat, and eventually resulted in the outer coat rupture at 90 minutes. It could be seen from the confocal images that, after 110 minutes, the outer coat almost completely dissolved, but some of the inner HPMC coat still remained on the pellet core.

![Confocal images of the HPMC sub-coated pellets in pH 5.5 phosphate buffer after 2 hours in pH 1.2 HCl](image)

**Figure 4.6.** Confocal images of the HPMC sub-coated pellets in pH 5.5 phosphate buffer after 2 hours in pH 1.2 HCl
Chapter 3 showed the coat dissolution process of the control-coated pellets, with the coat rupture time at 110 minutes (Section 3.13.1). Compared with the control-coated pellets, the time for the outer coat of the HPMC sub-coated pellets to rupture was shorter, 90 minutes. This early rupture of the outer coat would allow the earlier release of active ingredients, which could explain the shorter drug release lag time from the HPMC sub-coated prednisolone tablets, compared to the control-coated tablets. In addition, the complete dissolution of the outer coat from the HPMC sub-coated pellets was also earlier than the control-coated pellets, with 110 and 140 minutes respectively. This contributed to the faster drug release after the lag time. However, 5 mg/cm^2 HPMC sub-coat retarded the drug release, compared to 1 and 3 mg/cm^2 sub-coat. This is likely because that thick HPMC sub-coat generated a high viscous diffusion layer which inhibited the drug release.

The CLSM results also demonstrated that the coat dissolution mechanism of the HPMC sub-coated system was different from that of the Eudragit® L 30 D-55 double-coated system. Although the inner coat of the HPMC sub-coated system also dissolved before the outer coat, the dissolution process after the inner coat dissolution was different from the double-coated system. Shortly after the dissolving of the inner coat, the outer coat of the double-coated system exhibited fast dissolution (as shown in Section 3.13.1). However, the outer coat dissolution of the HPMC sub-coated system was not significantly accelerated. The earlier outer coat rupture of the HPMC sub-coated system was caused by the swelling of the hydrophilic inner coat polymer, thus resulting in the faster drug release.

_Influence of salts on drug release from HPMC sub-coated formulation_

It has been established that the coat dissolution mechanisms of the HPMC sub-coated system and the Eudragit® L 30 D-55 double-coated system are different. However, since there were salts presented in the inner coat of the double-coated system, the fair comparison would be the addition of salts in the HPMC sub-coating
layer. Figure 4.7 shows that in the presence of 10% sodium citrate in the HPMC layer, the drug release rate was accelerated from the HPMC sub-coated tablets with a sub-coat thickness of 5 mg/cm², compared to the control-coated tablets. This is different from the inhibition of drug release from the HPMC sub-coated tablets without sodium citrate in the sub-coat and with the same sub-coat thickness (as shown in Figure 4.4). This highlighted the possible impact of ionic strength and osmotic pressure in the inner coat on drug release.

![Graph showing drug release profiles](image)

**Figure 4.7.** Comparison of drug release profiles of the Eudragit® L 30 D-55 double-coated prednisolone tablets with the HPMC sub-coated tablets in pH 5.6 phosphate buffer after pre-treatment in pH 1.2 HCl for 2 hours.

It is deducible that during dissolution testing, upon exposure to the imbibed buffer medium, sodium citrate in the sub-coat dissolved. This increased the ionic strength and osmotic pressure of the inner coat, which likely accelerated the dissolution process of Eudragit® L 30 D-55 outer coat. Zhang et al. (2003) also reported that the inclusion of NaCl in the HPMC sub-coat could create an osmotic pump for drug
release from Eudragit® RS/RL coated tablets. However, since Eudragit® RS and RL are insoluble, drug release from this system was caused by the diffusion through the polymer coat. Therefore, drug release was only driven by osmotic pressure gradient between the HPMC sub-coat and the external dissolution medium. The increased ionic strength in the sub-coat due to the presence of NaCl has no effect on drug release rate.

The present study with the HPMC sub-coated Eudragit® L 30 D-55 enteric coating showed that, the presence of salt in the sub-coat changed the coat dissolution mechanism. The coat dissolution changed from simple inner coat swelling to the similar mechanism as for the Eudragit® L 30 D-55 double-coated system, which was driven by the increased ionic strength and osmotic pressure of the inner coat. The HPMC solution used for sub-coating has a high pH value of 7, due to the neutral nature of the polymer. However, drug release from the HPMC sub-coated tablets with 10% sodium citrate in the sub-coat was still slower than from the Eudragit® L 30 D-55 double-coated tablets, having 10% citric acid in the inner coat and neutralized to pH 6.0 (Figure 4.7). This is likely because in the double-coated formulation, a buffer system was generated by the partial neutralization of organic acid in the inner coat. However, there was an absence of this buffer system in the HPMC sub-coat. In addition, the Eudragit® L 30 D-55 polymer in the inner coat of the double-coated system was also partially neutralized. The acid groups of the polymer formed salts which also contributed to the buffer system.

It is also presumable that the Eudragit® L 30 D-55 inner and outer coat of the double-coated system have high compatibility and miscibility, due to the application of the same polymer. This could also contribute to the faster drug release from the double-coated system than from the HPMC sub-coated system. In general, the inner coat polymer of the double-coated system could be changed from partially neutralized Eudragit® L 30 D-55 to other hydrophilic polymer. However, the
Eudragit® L 30 D-55 double-coated system was still more advantageous compared to other inner coat polymer.

4.4.2 The roles of inner coat ionic strength and buffer capacity on the double coating dissolution

4.4.2.1 Influence of salts and acids on the dissolution of Eudragit® L 30 D-55 polymer

The increase of the inner coat ionic strength and buffer capacity of the double-coated system was due to the presence of salt and acid in the inner coat. Therefore, to evaluate the roles of the inner coat ionic strength and buffer capacity on the double coating dissolution, the effect of the presence of these salts and acids on the dissolution behaviour of Eudragit® L 30 D-55 polymer was firstly investigated.

Influence of salts

The influence of salts on the dissolution of Eudragit® L 30 D-55 polymer was represented and illustrated by the titration curves of the polymer with and without the presence of 15% sodium citrate (Figure 4.8). The pH of the original Eudragit® L 30 D-55 dispersion was 3.0. By adding 1 M NaOH into the dispersion, the pH of the dispersion increased. As illustrated by the titration curve of pure Eudragit® L 30 D-55, below pH 5.7, the pH of the dispersion increased very fast by adding very small amounts of 1 M NaOH. At these low pH values, the ionization and dissolution level of the polymer was very low. Starting from pH 5.7, the increase of the dispersion pH became very slow by adding 1 M NaOH, due to the quick dissociation and dissolution of the polymer. Until pH 5.8, all of the polymer particles in the dispersion dissolved, and the dispersion turned to a clear solution. After this pH
point, the increase of the dispersion pH by the amount of 1 M NaOH consumed became a smooth curve.

![Titration curves of Eudragit L 30 D-55 with and without sodium citrate.](image)

*Figure 4.8. Titration curves of Eudragit® L 30 D-55 with and without sodium citrate.*

At each pH values of the titration curve, given the amount of 1 M NaOH consumed by the dispersion, the neutralization degree of the polymer could be calculated based on the acid value of the polymer. It is described by the producer that 300-330 mg KOH is consumed to completely neutralize the methacrylic acid groups of 1 g Eudragit® L 30 D-55 polymer (Technical bulletin, 2005, Degussa Röhm Pharma Polymers). The polymer neutralization curves of Eudragit® L 30 D-55 formulations were then plotted (Figure 4.9). For pure Eudragit® L 30 D-55, the neutralization value below pH 5.7 was very low, which resulted in the limited polymer dissolution. From pH 5.7 to 5.8, the degree of polymer neutralization sharply increased because of the very slow increase of the dispersion pH by adding 1 M NaOH.
Compared to the titration curve of pure Eudragit® L 30 D-55, Eudragit® L 30 D-55 dispersion containing 15% sodium citrate exhibited slower pH increase at pH values lower than 5.7 (Figure 4.8). This is due to the gradual dissolution of the polymer above pH 5.4. Therefore, different from pure Eudragit® L 30 D-55 which showed a slow increase in the neutralization value at low pH and sharp increase from pH 5.7 to 5.8, sodium citrate-containing formulation presented a smooth neutralization curve from pH 5.4-5.8 (Figure 4.9). In the presence of sodium citrate, the polymer exhibited a higher ionization and dissolution speed at these low pH values compared to the pure Eudragit® L 30 D-55. After pH 5.8, due to the fact that all of the polymer has dissolved, the presence of sodium citrate had no further influence on the following titration or neutralization process.

From the above neutralization curves, it is evident that the dissolution speed of Eudragit® L 30 D-55 was accelerated by the presence of salt in the formulation at
lower pH values. One can deduce that this acceleration is associated to the increased ionic strength of the formulation.

Influence of acids

Having established the influence of salts on the dissolution of Eudragit® L 30 D-55, to elucidate the effect of organic acid on the polymer dissolution, titration curves of Eudragit® L 30 D-55 containing benzoic, adipic and citric acid, which have one, two and three acid groups respectively, were conducted (Figure 4.10). In the presence of organic acids, the consumption of 1 M NaOH were higher than pure Eudragit® L 30 D-55 at the same pH value, indicating that organic acid in the formulation was also neutralized by the addition of 1 M NaOH. Like sodium citrate-containing formulation, the presence of organic acid in the dispersion accelerated the dissolution of Eudragit® L 30 D-55 polymer at low pH values, reflected by the gradual dissolution of the polymer from pH 5.4.

![Titration curves of Eudragit® L 30 D-55 with different organic acids.](image)

*Figure 4.10. Titration curves of Eudragit® L 30 D-55 with different organic acids.*
It is noteworthy that unlike the pure polymer which dissolved completely until pH 5.8, Eudragit® L 30 D-55 dispersion changed to a clear solution with complete dissolution of the polymer particles at a lower pH point for organic acid-containing formulations (pH 5.6). This further supports the acceleration of the polymer dissolution speed at low pH values due to the presence of organic acid. Furthermore, organic acid was partially neutralized in the system and contributed to a buffer system which diminished the pH increase of the dispersion during the addition of 1 M NaOH, whereas, the ionization and dissolution of Eudragit® L 30 D-55 polymer continued. It is speculated that until the ionization and dissociation level of the polymer achieved certain point, the polymer completely dissolved.

The neutralization curves of Eudragit® L 30 D-55 in the presence of salt and organic acid also correlated to the drug release results from the double-coated tablets as shown in Chapter 3 (Section 3.5.3). The neutralization curves demonstrated that the acceleration of the polymer dissolution by the presence of salt and organic acid took place at lower pH values. Drug release from the double-coated tablets was also significantly accelerated compared to the control-coated tablets at pH values from pH 5.0 to 5.8. However, at pH values above 5.8, the acceleration was limited due to the already high drug release rate from the control-coated tablets.

**4.4.2.2 Calculation of the ionic strength and buffer capacity of the inner coat formulations**

Due to the partial neutralization of organic acids in the Eudragit® L 30 D-55 formulations, the ionic strength and buffer capacity of the formulations were both increased. To calculate the actual values of the ionic strength and buffer capacity of a given formulation, one needs to understand the percentage neutralization of the polymer and the organic acid in the formulation at a given pH. However, the acid groups of Eudragit® L 30 D-55 polymer and the organic acid were neutralized at the same time by the addition of 1 M NaOH. It is not possible to calculate the absolute
neutralization value of the polymer at a certain pH, due to the similarity of the pKₐ values of the methacrylic monomer of Eudragit® L 30 D-55 and the organic acids. This similarity results in the complexity of the proportion of 1 M NaOH consumed by the methacrylic acid groups of the polymer and the organic acid in the system.

Despite the difficulty to calculate the neutralization value of the polymer and the acid at every pH point of the neutralization curve, it is possible to obtain these values at pH 5.6. This pH value is distinguished from other pH because the polymer in the dispersion completely dissolved at pH 5.6. To perform this calculation, firstly, it is necessary to understand the determining factors of the solubility of weak acids. The solubility of weak acids is dependent on their ionization constants, Kₐ and the pH of the dissolution medium. At pH values more than one unit below pKₐ, the solubility of the acid is approximated by its intrinsic solubility which is equal to the solubility of its free acid. As the pH value increases, the solubility of the acid increases due to the contribution from the ionized form (Horter and Dressman, 2001). The solubility of an acid at a certain pH value could be approximated using Equation 2.

\[ S = (1 - n)S_a + nS_i \]  

Eq. 2

S = solubility of the weak acid;
S_a = solubility of its free acid;
S_i = solubility of the ionized form of the acid;
n = percentage neutralization of the acid at a given pH.

Since S_a and S_i are constant for a given acid, it is evident that the solubility of the acid at a certain pH is determined by its percentage neutralization. Eudragit® L 30 D-55 polymer is also a weak acid. During the neutralization by 1 M NaOH, at the pH point where the complete dissolution of the polymer occurred, a saturated
polymer solution was formed. Thus, the solubility of the polymer at this pH was achieved, and was equal to the concentration of the dispersion. Therefore, pure Eudragit® L 30 D-55 formulation and organic acid-containing formulation exhibited the same solubility at pH 5.8 and 5.6 respectively because they had the same polymer concentration of 15%.

Given the above understanding of the solubility of weak acids, if two formulations of a certain acid have the same solubility at a certain pH, the neutralization value of the acid in these two formulations is identical. Therefore, the percentage neutralization of Eudragit® L 30 D-55 in formulations with and without organic acid is the same at pH 5.6 and 5.8 respectively. The neutralization curve showed that, 28.5% polymer was neutralized for pure Eudragit® L 30 D-55 formulation to turn to a clear solution at pH 5.8. It was then postulated that the same polymer neutralization value was needed to completely dissolve it in 15% citric, adipic and benzoic acid-containing formulations at pH 5.6. Based on this postulation, the amount of 1 M NaOH consumed by the methacrylic acid groups of the polymer and the organic acid in the formulation and the resultant neutralization value of the polymer and the acid at pH 5.6 could be calculated. Table 4.2 shows the pKₘ values of the methacrylic acid monomer and the organic acids, as well as the percentage neutralization values of the polymer and the acids in the formulation.

The dissociation ratio of weak acid HA to its conjugate base A⁻ at different pH follows the Henderson-Hasselbalch (HH) equation: $pH = pK_a - \log \frac{[HA]}{[A^-]}$. The percentage neutralization values of benzoic, adipic and citric acid at pH 5.6 as shown in Table 4.2 comply the HH equation. Using benzoic acid as an example, according to the HH equation, 99% of benzoic acid should be neutralized at pH 6.42 ($pK_a + 2$). The calculated neutralization value of benzoic acid at pH 5.6 was 92.3% which is in the range of the values according to the HH equation. However, due to the presence of Eudragit® L 30 D-55 polymer, having a $pK_a$ of 4.46 for the
methacrylic monomer, in the dispersion, the neutralization ratio of the acids is more complicated than that is predicted by the HH equation. This is particularly the case for adipic acid and citric acid which have more than one pKₐs.

**Table 4.2.** pKₐ values and percentage neutralization of Eudragit® L 30 D-55 polymer and organic acids at the pH where complete polymer dissolution occurred

<table>
<thead>
<tr>
<th>Formulations</th>
<th>pKₐ of acids</th>
<th>Polymer dissolution pH</th>
<th>% Neutralization of polymer at dissolution pH</th>
<th>% Neutralization of organic acids at dissolution pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure Eudragit® L 30 D-55 (methacrylic monomer)</td>
<td>4.46</td>
<td>5.8</td>
<td>28.5</td>
<td>-</td>
</tr>
<tr>
<td>15% Benzoic acid</td>
<td>4.42</td>
<td>5.6</td>
<td>28.5</td>
<td>92.3</td>
</tr>
<tr>
<td>15% Adipic acid</td>
<td>4.41</td>
<td>5.6</td>
<td>28.5</td>
<td>70.1</td>
</tr>
<tr>
<td></td>
<td>5.41</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15% Citric acid</td>
<td>4.76</td>
<td>5.6</td>
<td>28.5</td>
<td>66.6</td>
</tr>
<tr>
<td></td>
<td>6.4</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Based on the calculation of the percentage neutralization of different organic acids in the inner coat formulations at pH 5.6, the ionic strength of the salts formed from these organic acids could be calculated. Table 4.3 shows the ionic strength of the inner coat formulations containing 15% citric acid, adipic acid and sodium citrate respectively. In addition, the buffer capacities of 15% citric and adipic acid formulations at pH 5.6 were measured and also listed in Table 4.3.
Table 4.3. Ionic strength and buffer capacities of different inner coat formulations at pH 5.6

<table>
<thead>
<tr>
<th></th>
<th>Citric acid (66.6% neutralized)</th>
<th>Adipic acid (70.1% neutralized)</th>
<th>Na citrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ionic strength</td>
<td>0.192</td>
<td>0.139</td>
<td>0.288</td>
</tr>
<tr>
<td>Buffer capacity (mmol/L/pH unit)</td>
<td>30</td>
<td>30</td>
<td>-</td>
</tr>
</tbody>
</table>

4.4.2.3 The roles of inner coat ionic strength and buffer capacity on the dissolution of the double-coated system

Effects of ionic strength

As confirmed by the influence of salts on the dissolution of Eudragit® L 30 D-55 polymer, increasing the ionic strength of the formulation accelerated the dissolution of the polymer. Effects of ionic strength on the dissolution of weak acids or acidic polymers have been reported in the literature. Nelson (1958) showed that the admixture with tribasic sodium phosphate could increase the dissolution rate of weak acids. Drug release from Eudragit® S coated pellets has also been reported as ionic strength dependent; drug release rate increased by increasing the ionic strength of the dissolution medium (Kararli et al., 1995).

The influence of ionic strength on the dissolution of weak acid and acidic polymer can be explained by the theory that the presence of ions in a solution can have a profound effect on the reaction rate between the reactants, by determining the activity coefficient of ions involved in the reaction (Moore and Pearson, 1981). The reaction rate increases by increasing ionic strength. Therefore, it is deducible that the ionization and dissociation rate of the carboxylic acid groups of Eudragit® polymer could be enhanced by increasing ionic strength.
In the case of the dissolution of polymer films, there was another theory that as the carboxylic acid groups of enteric polymer ionized, the repulsion of the charges forces the polymer film to expand (Zatz and Knowles, 1970). The presence of salts weakens the charge repulsion and compresses the charged film. This renders a high surface pressure on the film which forces the ionized groups to leave the film surface at a higher rate.

Aside from the influence of ionic strength, Spitael and Kinget (1977a) applied general base catalysis, which obeys Bronsted catalysis law, on the dissolution of anionic polymers. The anionic polymers dissolve through the dissociation of the carboxylic acid groups of the polymer by proton transfer to water molecules, resulting in the formation of the conjugate base of the polymer and hydronium ions (Equation 3).

\[
\begin{array}{c}
\text{R-CO-OH} \\
\end{array} \rightarrow \begin{array}{c}
\text{R-CO-O}^- + \text{H}_3\text{O}^+
\end{array}
\]  

Eq. 3

A general base makes the proton transfer easier by activating the oxygen atom of the water molecule with extra electrons by pulling a proton from it (Bender and Brubacher, 1973). Equation 4 shows that the base accepts a proton from the attacking water and consequently weakens the bond between the oxygen atom of the water molecule and the leaving proton. Thus the oxygen atom of the water molecule becomes more negatively charged, and its ability to accept a proton from the carboxylic acid group of the polymer is enhanced (Bender and Brubacher, 1973).

\[
\begin{array}{c}
\text{R-CO-OH} \\
\end{array} \rightarrow \begin{array}{c}
\text{R-CO-O}^- + \text{H}_3\text{O}^+ + \text{A}^-
\end{array}
\]  

Eq. 4
Regarding the double-coated system, sodium salts of organic acids in the inner coat dissolved upon exposure to the influx buffer medium. The presence of these salts would accelerate the dissolution rate of the outer Eudragit® L 30 D-55 coat, assuming that ions in the inner coat would migrate toward the outer coat during dissolution process. Once these ions came into contact with the outer coat polymer, the outer coat started to dissolve from inside due to the assistance of the increased ionic strength. This contributed to the fast dissolution of the double-coated system and the corresponding drug release.

Effects of buffer capacity

The influence of buffer capacity on the dissolution of ionizable drugs and polymers has been discussed in the literature (Shek, 1978; Spitaël et al., 1980; Ozturk et al., 1988b; Fadda and Basit, 2005; Ibekwe et al., 2006a). The determining factor for the dissolution rate of an acidic polymer is not the bulk buffer pH but the microenvironment pH adjacent to the dissolving polymer. Due to the generation of protons at the surface of the dissolving polymer, this microenvironment pH could be 0.2-0.6 unit lower than the bulk pH (Ozturk et al., 1988a; Harianawala et al., 2002). In an unbuffered dissolution system, the decrease of the pH in the boundary layer is dependent on the pKₐ and solubility of the acidic polymer (Ozturk et al., 1988b). However, in a buffered medium, this pH decrease is suppressed by the reaction of the acid polymer with the basic buffer salt, depending on the buffer capacity of the basic salt.

As acidic polymers, the dissolution rate of enteric polymers is significantly determined by the buffer capacity of the dissolution medium. Regarding the Eudragit® L 30 D-55 double-coated system, as shown in Table 4.3, the buffer capacities of the inner coat formulations are relatively high (30), which is higher than the buffer capacity of 0.05 M phosphate buffer (23). It is thus speculated that
the buffer capacity in the inner coat played a profound role in assisting the
dissolution of the Eudragit® L 30 D-55 outer coat, assuming the migration of the
ions from the inner coat to the outer coat.

**Distinguishing the roles of ionic strength and buffer capacity**

The above discussion established that buffer capacity and ionic strength independently contribute to increasing the dissolution rate of Eudragit® L 30 D-55 polymer and corresponding drug release. Although it has been reported in a few studies in the literature that drug release from acidic polymer coatings increased with increasing the buffer strength of the dissolution medium, the roles of buffer capacity and ionic strength have not been clearly distinguished in most of these cases (Hayashi et al., 1970; Ozturk et al., 1988a; Chan et al., 2001). Fadda and Basit (2005) has speculated that buffer capacity has more prominent influence compared to ionic strength on the dissolution profiles of Eudragit® S coated tablets. However, it was also pointed by the authors that buffer capacity seems to come into play after the coat starts to dissolve, and it has little influence on the lag time of drug release.

In the case of the double-coated system, upon exposure to the influx buffer medium, with the assistance of the salts in the inner coat, the Eudragit® L 30 D-55 outer coat starts to dissolve from inside. The ionic strength of the inner coat is the primary determining factor of the outer coat dissolution at this stage. After the outer coat starts to dissolve, the acidity of the polymer tended to decrease the pH inside the coat. The buffer capacity of the inner coat then starts to play an important role to maintain the crucial pH for the outer coat to dissolve from inside.

The distinct effects of ionic strength and buffer capacity of the inner coat could be demonstrated by comparing double-coated formulations with different inner coats. Figure 4.11 compared the drug release profiles of Eudragit® L 30 D-55 double-coated prednisolone tablets with 10% citric acid, sodium citrate or adipic
acid in the inner coat (all the formulation neutralized to pH 5.6), in pH 5.6 phosphate buffer after 2 hours in pH 1.2 HCl.

![Graph showing drug release profiles](image)

**Figure 4.11.** Comparison of drug release profiles of the Eudragit\textsuperscript{®} L 30 D-55 double-coated prednisolone tablets with 10% citric acid, sodium citrate or adipic acid in the inner coat in pH 5.6 phosphate buffer after pre-treatment in pH 1.2 HCl for 2 hours.

As shown in Table 4.3, adipic acid formulation had lower ionic strength than citric acid and sodium citrate formulation, which contributed to a longer drug release lag time. However, compared to the sodium citrate formulation, there was a buffer system in the adipic acid formulation with a high buffer capacity. After the outer coat polymer started to dissolve, the high buffer capacity of the inner coat of the adipic acid formulation allowed the polymer dissolution at a high speed, which reflected by the high drug release rate after the lag time.

Sodium citrate and citric acid formulation demonstrated the same drug release lag time, but the dissolution after the lag time was slower for sodium citrate formulation.
compared to citric acid formulation. This is likely due to the lack of buffer capacity in the sodium citrate-containing inner coat, and thus the decrease of the microenvironment pH inside the outer coat suppressed the further ionization of the polymer.

4.4.3 Migration of sodium ions from the inner to the outer coat during dissolution process

It has been established that the buffer system and the increased ionic strength caused by the partial neutralization of organic acids in the inner coat have significant effects on accelerating the dissolution of the outer Eudragit® L 30 D-55 coat. However, it is only possible for the ions in the inner coat to assist in the outer coat dissolution when presuming that the ions migrated from the inner coat into the outer coat during dissolution. To prove this ion migration hypothesis, the distribution of sodium ions throughout the coat of the double-coated system at different time points during dissolution testing was investigated using scanning electron microscopy/energy dispersive X-ray spectroscopy (SEM/EDX).

Coated pellets were used due to the easier examination under microscopy than tablets. The SEM pictures of the cross-section of the double-coated pellets in different time points after exposure to pH 5.5 phosphate buffer show the physical changes of the film coat during dissolution testing (Figure 4.12). These results correlate well with those obtained from CLSM tests (as shown in Chapter 3, Section 3.13.1). Both the inner coat and the outer coat of the double-coated pellets remained intact in pH 5.5 phosphate buffer during the first 30 minutes. Holes were seen in the inner coat after 35 minutes, and dominated the whole structure of the inner coat after 40 minutes due to its fast dissolution and gel formation. This followed by the distortion and dissolution of the outer coat. Until 55 minutes, only very small section of the coat remained on the pellet surface.
Figure 4.12. Scanning electron micrographs of the double-coated pellets at different time points in pH 5.5 phosphate buffer.
Figure 4.13 shows the sodium ion distribution throughout the coat in the cross-section of the double-coated pellets after removal from pH 5.5 phosphate buffer at different time points by EDX mapping (the black dots represent sodium ions). SEM pictures showed that after 45 minutes in pH 5.5 phosphate buffer, the coat of the pellets was not complete due to the dissolution of the outer coat. The EDX determination for these pellets was then carried out with the remaining intact part of the coat.

Before testing in buffer, the inner coat of the double-coated pellets was distinguished from the outer coat in the EDX mapping image due to the highly concentrated sodium ions. The sodium ions in the pellet core were likely contributed by the sodium migration into the core during the aqueous coating process of the inner coat. Within the first 30 minutes in pH 5.5 buffer, sodium ions remained in the inner coat. After 35 minutes, blank areas were seen in the inner coat which is likely due to the presence of holes. At 40 minutes, the area with concentrated sodium ions expanded toward the outer coat, indicating the migration of sodium ions from the inner coat to the outer coat. Sodium ions migrated further into the outer coat after 45 minutes in buffer and distributed homogeneously throughout the whole coat after 50 minutes.

Figure 4.14 shows the mass percentage of sodium in the different sections of the coat after the double-coated pellets were removed from pH 5.5 phosphate buffer at different time points. Section 1 and 2 represent the pellet core. The sodium concentration was constant during the dissolution process (data not shown).
Figure 4.13. EDX images of sodium ions distribution in the cross-section of the double-coated pellets after removal from pH 5.5 phosphate buffer at different time points.
Figure 4.14. The concentration of sodium ions in different sections of the coat of the double-coated pellets after removal from pH 5.5 phosphate buffer at different time points.

Sections 3-6 showed similar sodium concentration (5-6%) before testing in buffer, indicating that these sections represent the location of the inner coat. The sodium concentration remained constant in these inner coat sections at the first 30 minutes in buffer, and started to decrease after this time point. Rapid decrease of sodium concentration in these sections was seen from 40 to 55 minutes, with the concentration dropping from 4-5% to 1-2%. Section 7 showed lower sodium concentration than sections 3-6 but higher than sections 8-9 in the original coat, indicating that this section was located at the interface of the inner and the outer coat. The sodium concentration in section 7 increased to the same concentration as section 6 after 35 minutes in buffer and then decreased at the same rate as sections 3-6 in the following time points. This indicates that sodium ions migrated from the inner coat to this film coat interface and moved outward to the outer coat.
Sections 8-10 which are located in the outer coat showed no sodium ions during the first 35 minutes in buffer and started to exhibit increased sodium concentration at 40, 45 and 50 minutes for section 8, 9 and 10 respectively. These time points represented the time needed for the sodium ions to migrate from the inner coat to these outer coat sections. After 50 minutes in pH 5.5 buffer, all the sections from section 3 to section 10 achieved similar sodium concentration, which indicates that sodium ions distributed homogenously throughout the film coat.

These results of sodium concentration in different sections of the coat at different time points correlate well with EDX images of the sodium distribution at the same time points during dissolution testing. The results also correlate well with the coat dissolution process revealed by both the CLSM testing and SEM images. After 35-40 minutes in buffer, buffer medium penetrated through the outer Eudragit® L 30 D-55 coat and dissolved the water soluble inner coat. The sodium ions in the inner coat then started to migrate into the outer coat which together with the migration of other ions contributed to a buffer system and increased the ionic strength in the outer coat and thus accelerated the outer coat dissolution.

4.4.4 The role of inner coat osmotic pressure on drug release from the double-coated system

4.4.4.1 Determination of inner coat osmotic pressure

The hypothesis of the influence of inner coat osmotic pressure on drug release from the double-coated system is that, the osmotic pressure in the inner coat can drive more influx buffer medium into the system, thus accelerating the outer coat dissolution. The application of osmotic pressure as the driving force for drug release from controlled-release systems has been well established in the literature (Zentner et al., 1985a; Zentner et al., 1985b; Ozturk et al., 1990; Thombre et al., 2004; Philip and Pathak, 2006; Ende and Miller, 2007). These osmotic pump systems typically
consist of porous semi-permeable membrane coat applied on a core comprising osmotic agent. After the influx dissolution medium dissolves the osmotic agent in the core, the osmotic gradient between the core and the external medium forces constant drug diffusion through the pores of the coat.

For osmotic pump drug release systems, the osmotic pressure of the core is constant due to the presence of a large amount of osmotic agent such as mannitol, sucrose or sodium chloride (Ozturk et al., 1990; Jonnalagadda and Robinson, 2000; Zhang et al., 2003). For the Eudragit® L 30 D-55 double-coated system, due to the limited amount of salts in the inner coat, the osmotic pressure generated in the inner coat possibly decreases when increasing the exposure time to buffer because of the increasing amount of influx buffer medium. However, the osmotic pressure in the inner coat after 2 hours acid treatment could be determined based on the amount of acid absorbed by the inner coat.

Table 4.4 shows the percentage and amount of acid taken by the control-coated and the double-coated glass beads. The percentage of acid uptake by the inner coat of the double coating was calculated by deducing the acid uptake of the double coating by that of the control coating. The amount of acid taken by the inner coat of the double-coated formulation containing 10% citric acid in the inner coat and neutralized to pH 5.6 was then calculated. It has been shown in Table 4.2 that 66.7% citric acid in the inner coat was neutralized at pH 5.6. Based on this neutralization percentage and the quantity of acid in the inner coat, the concentration of citric acid and sodium citrate in the inner coat after 2 hours acid treatment were calculated as 48.4 and 96.8 mg/ml respectively. The same were calculated for the 10% adipic acid-containing inner coat formulation, with adipic acid and sodium adipate concentration of 43.3 and 101.6 mg/ml respectively, given the percentage neutralization of adipic acid as 70.1% (as shown in Table 4.2).
The osmotic pressure of these organic acids and salts at the above concentrations were measured (saturated solution for adipic acid were used, due to its low water solubility). The osmotic pressure of these two inner coat formulations after 2 hours acid treatment were given by the sum of the osmotic pressure of the presented acid and the corresponding salt for each formulation. The osmotic pressure values were 1275 and 2124 mOsmo/Kg H$_2$O for 10% citric acid and 10% adipic acid-containing inner coat formulation respectively.

Table 4.4. Acid uptake of the 10% citric acid double-coated and the control-coat glass beads after 2 hours in acid

<table>
<thead>
<tr>
<th></th>
<th>Control-coat</th>
<th>Double-coat</th>
<th>Inner-coat of double-coat</th>
</tr>
</thead>
<tbody>
<tr>
<td>% acid uptake based on the weight of beads</td>
<td>0.69</td>
<td>1.89</td>
<td>1.2</td>
</tr>
<tr>
<td>Amount of acid in the film coat (ml/cm$^2$)</td>
<td>1.78x10$^{-3}$</td>
<td>5.43x10$^{-3}$</td>
<td>3.45x10$^{-3}$</td>
</tr>
</tbody>
</table>

4.4.4.2 Influence of osmotic pressure on drug release

To illustrate the osmotic pressure driven drug release mechanism, it is commonly used to determine the drug release rate in dissolution media with different osmotic pressures. Drug release rate decreases by reducing the osmotic pressure difference between the core and the external environment (Zentner et al., 1985a; Ozturk et al., 1990; Philip and Pathak, 2006; Ende and Miller, 2007). Dissolution tests for the double-coated tablets with the above two inner coat formulations were conducted in pH 5.6 phosphate buffer with different urea concentrations following 2 hours in pH 1.2 HCl. Table 4.5 lists the osmotic pressure of these dissolution media and the differences between the inner coat and the test media. Figures 4.15 and 4.16 show the drug release profiles in these dissolution media.
Table 4.5. Osmotic pressure of pH 5.6 phosphate buffer with different urea concentrations and the osmotic pressure difference of the inner coat and dissolution media (mOsmo/Kg H₂O)

<table>
<thead>
<tr>
<th>Urea concentration (mg/ml)</th>
<th>Osmotic pressure of test medium (mOsmo/Kg H₂O)</th>
<th>Osmotic pressure difference of the inner coat and the dissolution medium (mOsmo/Kg H₂O)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>10% citric acid formulation</td>
</tr>
<tr>
<td>0</td>
<td>119</td>
<td>1156</td>
</tr>
<tr>
<td>0.5 M</td>
<td>604</td>
<td>671</td>
</tr>
<tr>
<td>1 M</td>
<td>1052</td>
<td>223</td>
</tr>
<tr>
<td>2 M</td>
<td>2277</td>
<td>-1002*</td>
</tr>
<tr>
<td>4 M</td>
<td>4430</td>
<td>-3155*</td>
</tr>
</tbody>
</table>

*: The minus values indicate the osmotic pressure of the test medium is higher than the inner coat of the double-coated formulation.

Figure 4.15. Drug release profiles of the Eudragit® L 30 D-55 double-coated prednisolone tablets with 10% citric acid in the inner coat in pH 5.6 phosphate buffer with different urea concentrations after pre-treatment in pH 1.2 HCl for 2 hours. (Due to the closeness of the curves, error bars are not shown.)
Figure 4.16. Drug release profiles of the Eudragit® L 30 D-55 double-coated prednisolone tablets with 10% adipic acid in the inner coat in pH 5.6 phosphate buffer with different urea concentrations after pre-treatment in pH 1.2 HCl for 2 hours. (Due to the closeness of the curves, error bars are not shown.)

Surprisingly, in contrast to the expected decrease of drug release by increasing the osmotic pressure of the test medium, drug release rate for both 10% citric acid and 10% adipic acid-containing formulations in general increased with increasing the medium osmotic pressure. This unexpected increase of drug release rate could be explained by the dissociation of urea into ammonia and cyanate in the buffer solution, which could increase the ionic strength of the test medium (Warner, 1942).

For the dissolution in media containing 0, 0.5, 1 and 2 M urea, as the urea concentration increases, the change of drug release rate was determined by the combination of the decrease of osmotic pressure gradient between the inner coat and the external medium and the increase of the medium ionic strength. However, in general, the ionic strength showed a more prominent influence compared to osmotic
pressure. The impact of ionic strength on drug release rate could be confirmed by the increase of the drug release rate in 4 M urea solution compared to 2 M urea solution, because the osmotic pressure had already no influence on the dissolution in these two urea concentrations.

Although it has been proved that there was osmotic pressure gradient between the inner coat and the test medium, unlike osmotic pump drug release systems, the influence of osmotic pressure gradient on drug release from the double-coated system was limited. For better understanding these drug release results, weight changes of the film coat of the double-coated glass beads with 10% citric acid-containing inner coat was determined in pH 5.6 phosphate buffer following 2 hours acid treatment (Figure 4.17). The results were also compared with that of the control-coated glass beads.

![Graph showing weight change of the coat of Eudragit® L 30 D-55 control-coated and double-coated glass beads in pH 5.6 phosphate buffer after 2 hours in pH 1.2 HCl.](image)

**Figure 4.17.** The weight change of the coat of the Eudragit® L 30 D-55 control-coated and double-coated glass beads in pH 5.6 phosphate buffer after 2 hours in pH 1.2 HCl.
The amount of buffer absorbed by the control-coat was very low during the first 35 minutes exposure to pH 5.6 phosphate buffer. The decrease of the coat weight indicated the dissolution of the film coat. In contrast, the weight of the double-coat increased upon exposure to buffer, indicating more buffer imbibed into the double-coat than the control-coat. The weight of the double-coat increased to the peak value after 20 minutes in buffer, followed by a slight decrease until 30 minutes. It was observed during the test that, some of the double-coat started to dissolve after 20 minutes in buffer, which contributed to the decrease of the film coat weight. After 30 minutes in buffer, all of the film coats of the double-coated beads started to dissolve and became tacky which stopped the further determination.

It is evident that the osmotic pressure in the inner coat drove higher amount of influx medium into the double-coated system compared to the control coating. However, the total amount of buffer imbibed into the double-coat before it started to dissolve was very low, maximum 12% based on the weight of the film coat. Furthermore, the dissolution of the double-coat was very fast upon exposure to the influx buffer medium, which limited the extent of the influence of the osmotic pressure on the coat dissolution. The osmotic pressure in the inner coat may contribute to the initial buffer influx, but it is not essential for accelerating the drug release rate from the double-coated system.

4.4.5 General discussion of the dissolution mechanism of the double-coated system

The fast drug release from the double-coated system was caused by the accelerated dissolution rate of the outer coat. This is attributable to the increased ionic strength and buffer capacity of the inner coat, and the migration of ions from the inner to the outer coat. The outer coat dissolution of the double-coated system is the result of two parallel processes. The first process is the penetration of buffer medium through the outer coat into the inner coat, resulting in the fast dissolution of the water soluble
inner coat. The dissolved organic acids and salts in the inner coat then start to migrate toward the outer coat. With the assistance of these acids and salts, the outer Eudragit® L 30 D-55 coat starts to dissolve from inside. The second process is the dissolution of the outer coat from outside in contact with the external buffer medium.

Figure 4.18 illustrated the changes of the film coat as a result of these processes. The diagram defines different film thicknesses: the initial physical film thickness, \( l_o \); the thickness of film with migrated acids and salts, \( l_m \); the thickness of film dissolved from outside, \( l_{d1} \); the thickness of film dissolved from inside, \( l_{d2} \); the instantaneous physical film thickness, \( l_f \).

At any time of the dissolution process \( l_f \) can be given by Equation 5.

\[
l_f = l_o - l_{d1} - l_{d2}
\]

Eq. 5

From equation 5, the rate of changes of the remaining film thickness, \( \frac{dl_f}{dt} \), is determined by the rates of \( \frac{dl_{d1}}{dt} \) and \( \frac{dl_{d2}}{dt} \). For the rate of film dissolving from outside, the dissolved film is transferred away from the film-medium interface to the bulk medium. By mass balance, the molar flux of polymer away from the interface is equal to the molar loss of polymer film,

\[
C_p \frac{dl_{d1}}{dt} = -k_m (x_o - x_b)
\]

Eq. 6

where \( C_p \) is the molar density of the polymer, \( x_o \) is the mole fraction of polymer at the interface, \( k_m \) is the mass-transfer coefficient, and \( x_b \) is the mole fraction of polymer in the bulk medium (Ebel et al., 1993).
Figure 4.18. Schematic definition of the outer coat dissolution process of the double-coated system: the initial physical film thickness, \( l_o \); the thickness of film with migrated acids and salts, \( l_m \); the thickness of film dissolved from outside, \( l_{d1} \); the thickness of film dissolved from inside, \( l_{d2} \); and the instantaneous physical film thickness, \( l_f \).

The mass transfer coefficient \( k_m \) is dependent on the dissolution medium properties, such as pH, ionic strength and buffer capacity. Setting \( x_b \) in Equation 6 equal to zero for sink conditions gives Equation 7:
In the case of film dissolving from inside of the outer coat, the rate can not be defined using Equation 7, since there is no mass transfer in the inside of the coat. However, it is conceivable that $\frac{dl_{d1}}{dt}$ is dependent on the rate of acid and salt migration and the ionic strength and buffer capacity of the inner coat.

At low buffer pH, $\frac{dl_{d1}}{dt}$ is very low due to the very low $k_m$. Therefore, $\frac{dl_{d2}}{dt}$ is the dominant speed determining the whole process of the outer coat dissolution, which is reflected by the accelerated drug release rate from the double-coated tablets compared to the control-coated tablets in low buffer pH. At high buffer pH, $\frac{dl_{d1}}{dt}$ increases due to the increased $k_m$. Consequently, the significance of $\frac{dl_{d2}}{dt}$ on the dissolution process of the double-coated system reduces, rendering the similarity of drug release rate from the double-coated and the control-coated tablets.

4.5 CONCLUSION

The accelerated drug release from the double coating system was the result of the outer coat dissolution from both inside and outside of the coat. The inside dissolution of the outer coat was attributable to the increased ionic strength and buffer capacity of the inner coat and the migration of water soluble components from the inner to the outer coat during dissolution process. The inner coat osmotic pressure played a minor role in the dissolution of the double coating system.
CHAPTER 5

GENERAL DISCUSSION AND FUTURE WORK
5.1 GENERAL DISCUSSION AND CONCLUSIONS

Enteric coatings exploit the pH differential in the upper GI tract to deliver drugs to the small intestine. Enteric-coated products normally dissolve rapidly in the *in vitro* situation; however in vivo they can take up to 2 hours to disintegrate in the small intestine post gastric emptying. The focus of this study was to use formulation approaches to accelerate the dissolution of a conventional enteric coating based on the methacrylic acid ethyl acrylate copolymer – Eudragit® L 30 D-55 (aqueous) and Eudragit® L 100-55 (the organic system of the same polymer) in conditions simulating the upper small intestine. The work started with investigating the effect of incorporating pH-sensitive materials into Eudragit® L 30 D-55 and Eudragit® L 100-55 films on film dissolution. Low molecular weight organic acids and high molecular weight pH-sensitive polymers were explored.

Despite the pH-dependent properties of these materials, both low molecular weight acids and high molecular weight polymers leached out from the films in acid stage of the dissolution tests. The alteration of the film formation processes contributed to the leaching of the latter. The film dissolution rates in subsequent buffer were therefore not influenced by the incorporation of these additives. Physicochemical properties of the films were evaluated to obtain a fundamental understanding of the film dissolution properties through the employment of differential scanning calorimetry (DSC) and scanning electron microscopy/energy dispersive X-ray spectroscopy (SEM/EDX).

Although it was not feasible to accelerate film dissolution using the above approaches, interesting findings were obtained and stimulated further step of the study. It was established that partially neutralizing Eudragit® L 30 D-55 dispersion in the presence of organic acids brought out films with rapid dissolution when directly testing in buffer. However, during the necessary pre-treatment in acid medium (pH 1.2 HCl) for these enteric films, the high acidity of HCl caused ion
exchange between the medium and the films. This impeded their dissolution in subsequent buffer. Approaches that can protect their functional properties in acid medium were then investigated to preserve the rapid film dissolution in buffer.

A novel double-coated enteric system was designed by applying a normal Eudragit® L 30 D-55 coating (outer coat) on top of the above partially neutralized organic acid-containing film (inner coat) coated on a solid core. The design of this double-coated system is based on the hypothesis that the outer enteric coating can prevent the ion exchange of the inner coat in acidic medium. The potential of this double-coated system to accelerate the coat dissolution in buffer was then probed. Immediate release prednisolone tablets were coated with the novel double coating system or a normal single layer Eudragit® L 30 D-55 coating (control coating). Both the double coating and the control coating showed good acid-resistance. In subsequent phosphate buffer, drug release was substantially accelerated from the double-coated tablets compared to the control-coated tablets, especially at buffer pH from 5.0 to 6.0, resembling proximal small intestinal pH conditions.

The *in vitro* assessment of enteric coatings is usually conducted by dissolution testing in pH 6.8 phosphate buffer. However, this high buffer pH does not resemble proximal small intestinal pH conditions, nor is sufficient to differentiate the dissolution behaviours between different enteric coatings. It also contributes to an *in vitro*/*in vivo* discrepancy of the enteric coating performance. Applying dissolution tests in pH conditions simulating the proximal small intestine is therefore beneficial to discriminate different enteric coatings and predict their *in vivo* performance.

To achieve a deeper understanding of how the double coating accelerates the drug release, polymer dissolution velocity tests were conducted. This was carried out by applying the coating formulations on placebo glass beads and measuring the polymer dissolution rates from them using refractive index detection. At all of the buffer pH values applied for drug release testing Eudragit® L 30 D-55 polymer
dissolved faster from the double-coated than the control-coated glass beads. This explained the fast drug release from the double-coated tablets. Compared to drug release testing, polymer dissolution velocity testing can eliminate the influence of active substance and excipients in the core, thus providing a direct assessment and comparison of dissolution performance of different film coatings.

A further technique – confocal laser scanning microscopy was employed to give an insight to the dissolution mechanisms of the double-coated system by revealing the coat dissolution processes. Coated prednisolone pellets were applied for these tests. In contrast to the slow and gradual dissolution of the control coating, the double coating dissolved much earlier and faster and exhibited a distinct dissolution process. Buffer medium first penetrated through the outer coat and came into contact with the inner coat. The partially neutralized inner coat dissolved rapidly before the outer coat and substantially accelerated the dissolution speed of the outer coat. Confocal laser scanning microscopy proved to be a useful tool to probe the mechanisms and processes involved in the dissolution of enteric-coated formulations.

Great attention was given to the optimization of the double coating system. The influence of different formulation factors, such as outer coat thickness, acid species/concentrations in the inner coat and the inner coat neutralization values, on drug release from the double-coated tablets was exploited. The drug release lag time was reduced to 5 minutes from prednisolone tablets coated with the optimized double coating formulation at buffer pH simulating the upper small intestine (pH 5.6). The corresponding lag time from the control-coated tablets was 100 minutes. The drug release from this optimized double coating formulation was also evaluated in physiological bicarbonate buffer (at pH 6.8 and 7.4), and exhibited faster rate than the control-coated tablets. This provides further confidence for the expected rapid dissolution and disintegration of the double-coated system in vivo.
Having established the accelerated coat dissolution and drug release from the double-coated system, the rest of the study focused on achieving a fundamental understanding of the mechanisms involved in the double coating dissolution. Based on the CLSM results, factors that can impart the inner coat to assist in the dissolution of the outer coat were thoroughly investigated. The roles of the inner coat ionic strength and buffer capacity on the outer coat dissolution were identified and distinguished. The neutralized inner coat contains salts which contributed to an increased ionic strength. This activates the ionization of the anionic outer coat polymer governed by the Bronsted catalysis law. A buffer system is also generated by the presence of organic acid and its salt in the inner coat. The buffer capacity of the inner coat plays a profound role in suppressing the microenvironment pH decrease after the acidic outer coat polymer starts to dissolve.

However, the diffusion of the acids and ions from the inner coat into the outer coat is necessary for their assistance in the outer coat dissolution. This is supported by the migration of sodium ions in the double coating system illustrated by SEM/EDX testing. The inner coat osmotic pressure was found to have little influence on accelerating the outer coat dissolution. This may arise because the double coating dissolves rapidly upon exposure to the influx buffer medium, which limits the extent of the osmotic pressure influence on the coat dissolution.

In general, the dissolution of the outer coat of the double-coated system is the result of two parallel processes. The first process is the penetration of buffer medium through the outer coat into the inner coat resulting in its rapid dissolution. The dissolved organic acid and salts in the inner coat then start to migrate toward the outer coat. With the assistance of the acid and salts, the outer coat starts to dissolve from inside. The second process is the dissolution of the outer coat from outside in contact with the external buffer medium. At low buffer pH, the rate of the outer coat dissolution from outside, regulated by mass transfer, is low. Therefore, the high dissolution rate from inside due to the high ionic strength and buffer capacity of the
inner coat is the dominant factor determining the whole outer coat dissolution. As the buffer pH elevates, the dissolution rate from outside increases, thus consequently reducing the significance of the dissolution from inside.

The novel double-coated system is gastric-resistant and greatly accelerates the dissolution of a conventional enteric coating in conditions simulating the upper small intestine. It offers a means to provide fast drug release in the small intestine and overcome the limitations of conventional enteric coatings. This system could be extrapolated to other enteric and modified release systems based on pH-responsive polymers as they all have the same underlying dissolution mechanisms.
5.2 FUTURE WORK

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The Eudragit® L 30 D-55 double-coated system has shown satisfactory in vitro performance in conditions simulating the upper small intestine. It is important to assess the in vivo performance of this system compared to the conventional enteric coatings. This can be conducted by gamma scintigraphy study testing the disintegration time and site of the coated tablets.

***

This system can be extended to other enteric polymers based on pH-dependent dissolution. Both the inner and the outer coat can be exchanged with currently used cellulose-based enteric polymers or polyvinyl derivatives. It is of interest to compare the acceleration abilities of the double-coated system on the dissolution of different enteric polymers.

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The application of pH-responsive systems is one of the most appealing approaches for targeting drugs to the ileo-colonic region of the GI tract. Great interest has been expressed for the development of coating systems based on pH-dependent polymers which dissolve at the higher pH values of the distal small intestine and colon. Polymethacrylate polymers Eudragit® S and Eudragit® FS with dissolving pH of 7 have been most commonly chosen as coating materials for these systems. A number of products based on Eudragit® S coating are approved for therapy of inflammatory bowel disease, including Asocol® MR and the associated ethical generic, Mesren® MR and Ipocol® MR.
However, there have been reports of intact tablets coated with Eudragit® S in the faeces of some patients (Schroeder et al., 1987; Sinha et al., 2003). In addition, the site and time of disintegration of Asacol® tablets in human subjects are highly variable. The inconsistency in performance has been attributed to inter-subject variability in intestinal pH as well as the GI transit time (Ibekwe, 2006). The lack of free fluid in the colon (13 ± 12 ml in the fasted and 11 ± 26 ml in the fed state (Schiller et al., 2005)) also contributes to the slow dissolution of the Eudragit® S coating and the consequent failure of drug release.

Since these pH-dependent polymers have the same underlying dissolution mechanism, it is conceivable that the concept of the double-coated system can also be extrapolated to Eudragit® S and Eudragit® FS coatings for developing new colonic delivery systems. The assistance of the inner coat in the dissolution of the outer pH-dependent polymer can overcome the lack of fluid in the colon, thus improving the in vivo performance of these coating systems.
PUBLICATIONS ASSOCIATED WITH THE THESIS


The use of confocal laser scanning microscopy (CLSM) to investigate the coating dissolution processes of different enteric coating formulations. Fang Liu, Rosario Lizio, Hans-Ulrich Petereit, Peter Blakey, Abdul W. Basit. The AAPS Journal, (Abstract) Vol. 9 (S2), T2062
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259


262


268


