



Inhibiting the gastric burst release of drugs from enteric microparticles: the influence of drug molecular mass and solubility

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4 drug molecular mass and solubility
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3 Abstract
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7 Undesired drug release in acid medium from enteric microparticles has been widely
8 reported. In this paper we investigate the relative contribution of microparticle and drug
9 properties, specifically microsphere size and drug's molecular weight and acid solubility,
10 on the extent of such undesired release. A series of nine drugs with different
11 physicochemical properties were successfully encapsulated into Eudragit S and Eudragit L
12 microparticles using a novel emulsion solvent evaporation process. The process yielded
13 spherical microparticles with a narrow size distribution (25-60 μm and 35-55 μm for
14 Eudragit L and Eudragit S microparticles respectively). Upon incubation in acid medium
15 (pH 1.2) for 2 h, the release of dipyridamole, cinnarizine, amprenavir, bendroflumethiazide,
16 budenoside, prednisolone from both Eudragit microparticles was less than 10% of drug
17 load and conformed with USP specification for enteric dosage forms. In contrast, more than
18 10% of the entrapped paracetamol, salicylic acid and ketoprofen were released. Multiple
19 regression revealed that the drug's molecular weight was the most important factor that
20 determined its extent of release in the acid medium, while its acid solubility and
21 microsphere's size had minor influences.
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35 Keywords: Microspheres, delayed release, enteric polymers, methacrylic polymers, gastric
36 resistance, colonic delivery.
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INTRODUCTION

The last two decades witnessed the emergence of microencapsulation technology in pharmaceutical formulations^{1,2}, which provided a unique platform for delayed and site-specific oral drug delivery³. Modified release microparticles provide several advantages over conventional enteric and delayed release formulations such as larger surface area, potentially more uniform gastric emptying, and a more consistent drug release profile. Unfortunately, the particulate nature and large surface area are accompanied by a major challenge: the inhibition of drug release until the target site is reached. In *in vitro* dissolution tests, enteric formulations may release no more than 10% of their drug content during a two-hour incubation in 0.1N HCl, and subsequently should release more than 80% of their drug content within 45 min of changing the dissolution medium to intestinal conditions. While drug release in intestinal conditions is easily achieved given that readily suspended microparticles have a large surface area, minimising/inhibiting drug release in acidic conditions has proven challenging, and insufficient control of drug release from microparticles in acid media has been reported⁴⁻¹⁰.

It is commonly assumed that the microparticles' surface area is the major factor influencing drug release from matrix microparticles^{11,12}. This is in contrast to a previous report by our group which showed that reducing the size of Eudragit S microparticles by two thirds did not alter prednisolone release in the acidic medium¹³. Very little attention has been given to the chemical properties of the drug molecule itself. Silva and Ferreira⁷ used an empirical approach to explore the major factors affecting drug release from microparticles and suggested that high molecular weight and poor drug solubility in acid favours low drug release in acid medium. We have shown that the control of drug release was not necessarily influenced by drug distribution within the microparticle or by high drug solubility in acid¹⁴. Nevertheless, the relative importance of all these factors is still unclear.

The aim of the work described in this paper was therefore to explore the relative importance of three drug and particle properties that have been directly related to drug release in gastric conditions^{6,7,15}, namely, drug molecular weight and its solubility in acid, and microsphere size. Using an efficient o/o emulsion solvent evaporation method developed in our laboratory^{13,16}, small uniform-size microparticles loaded with one of nine drug molecules of different physicochemical properties were produced using two different

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3 pH responsive polymers; Eudragit S and Eudragit L (pH thresholds 7.0 and 6.0
4 respectively). In addition, multiple regression was used to investigate the relative
5 importance of the 3 drug/microsphere properties and to explore the limitations of pH
6 responsive matrix microparticles.
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10 11 12 **MATERIALS AND METHODS**

13 14 15 **Materials**

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17 Paracetamol was supplied by Knoll AG (Ludwigshafen, Germany) and prednisolone was
18 obtained from Sanofi-Aventis, (Romainville, France). Budesonide and amprenavir were
19 gifts from Astra Zeneca (UK) and GlaxoSmithKline (UK) respectively. Ketoprofen,
20 salicylic acid, dipyridamole, cinnarizine, bendroflumethiazide, sorbitan sesquioleate (Span
21 83, Arlacel 83) and liquid paraffin were purchased from Sigma-Aldrich, (Poole, UK).
22 Polymethacrylate polymers, Eudragit S and L, were generously provided by Evonik
23 Degussa Chemicals (Darmstadt, Germany).
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30 31 **Preparation of microparticles**

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33 Drug loaded Eudragit S or Eudragit L microparticles were prepared as reported
34 previously¹⁶. Briefly, 0.3 g of drug (indomethacin, paracetamol, salicylic acid, ketoprofen,
35 naproxen, prednisolone, budesonide, bendroflumethiazide, amprenavir or dipyridamole)
36 and 3 g of polymer (Eudragit S /L) were dissolved in 30 ml of absolute ethanol. The
37 resulting solution was emulsified into 200 ml liquid paraffin containing sorbitan
38 sesquioleate (Span 83) (1% w/w) as the emulsifier by stirring at a speed of 1000 rpm
39 (Heidolph RZR1 stirrer, Heidolph Instruments, Schwabach, Germany) for 18 hours at room
40 temperature. Solidified microparticles were collected by vacuum filtration, followed by
41 washing three times using fresh batches of 50 ml *n*-hexane. Due to cinnarizine's low
42 solubility in ethanol, the drug and the polymer (Eudragit S or Eudragit L) were dissolved in
43 30 ml of a mixture of ethanol: acetone (1:1 v/v) and microparticles were prepared as above.
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52 53 **Microspheres size analysis**

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55 The volume median diameter of each microparticle formulation suspended in 0.1N HCl
56 was measured in triplicate using laser light scattering using a Malvern Mastersizer 2000
57 with a 45mm lens (Malvern Instruments Ltd., Malvern, UK). Span of microsphere size was
58 calculated as $[D(v,0.9)-D(v, 0.1)] /D(v,0.5)$ where $D(v,0.9)$, $D(v,0.5)$ and $D(v,0.1)$ are the
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particle diameters at the 90th, 50th and 10th percentile respectively of the microsphere size distribution curve. Microsphere size analysis of each formulation was carried out in triplicate.

X-Ray Powder Diffraction

A Philips PW3710 Scanning X-Ray Diffractometer (Philips, Cambridge, UK) with a Cu K α filter generated at 30mA and 45 kV was used to characterize the drug loaded microparticles. Samples were placed in a round disc sample holder and gently compressed and smoothed using Perspex block. Samples were scanned at 0.02 °/sec from 5° to 45°. The peak was calculated using X'Pert HighScore data analysis software (version 2.0a).

Differential Scanning Calorimetry

A DSC 7 Differential Scanning Calorimeter (PerkinElmer Instruments, Beaconsfields, UK) calibrated with indium, was used to assess the presence of crystalline drug in Eudragit S and Eudragit L microparticles. Microparticles (3-5 mg) were accurately weighed and placed in non-hermetic aluminum pan. Before starting the thermo scan, an isothermal period at 100 °C (90°C for ketoprofen microparticles) was applied for 5 min (to eliminate residual water content), then the samples were cooled and scanned from 50 °C to 200 °C at a rate of 10 °C/min. Pyris Thermal Analysis Software was used to record and analyze the data.

Drug encapsulation efficiency in microparticles

Drug loaded microparticles (50 mg) were dissolved in 50ml methanol. The resulting solution was then diluted 10 times with HCl 0.1 N (for neutral and basic drugs) or with phosphate buffer pH 7.4 (for acidic drugs). Samples were filtered using a 0.22 μ m Millex filter and assayed spectrophotometrically. UV-Vis absorbance was measured using spectrophotometer at λ_{max} = 243, 301, 254, 245, 246, 254, 263, and 280 nm for paracetamol, salicylic acid, ketoprofen, prednisolone, budesonide, bendroflumethiazide, amprenavir, and dipyrindamole respectively. The encapsulation efficiency of cinnarizine was determined by dissolving 50 mg of microparticles in 50 ml methanol; 10 ml was taken and 0.1M HCl was added to precipitate the polymers and made up to 100 ml. Samples were filtered through 0.22 μ m Millex filters and 3.75 ml of the filtrate was added to 5 ml of acetonitrile followed by the addition of 1.25 ml of triphosphate buffer. Cinnarizine was assayed using Hypersil column Thermo Scientific (Runcorn, UK). A Hewlett-Packard 1050

series HPLC system (Agilent Technologies, UK) supplied with Waters 470 Millipore fluorescence detector (Milford, MA, USA) was utilized to detect samples. The mobile phase, consisting of acetonitrile (70% v/v) and 10 mM potassium dihydrogen phosphate buffer (30% v/v), was eluted at a flow rate of 1 ml/min. The injection volume was 10 μ l, and the fluorescence detector employed an excitation wavelength of 249 nm and emission wavelength of 311 nm.

For each formulation, 3 different batches were assessed. Drug encapsulation efficiency was calculated as:

$$\text{encapsulation efficiency} = \frac{\text{measured mass of drug in microparticles}}{\text{theoretical mass of drug in microparticles}} \times 100$$

Eq.1

Drug solubility in acidic medium

In order to assess the influence of the drug's solubility in acid on its release, the solubility of all encapsulated drugs in acidic medium were assayed. An excess amount of drug was added to 10 ml of HCl 0.1 N solution and shaken for 24 hours at 200 rpm and 37 °C. The saturated solutions were filtered (0.22 μ m Milleux syringe filters), diluted as appropriate, and UV absorbance was measured at λ_{max} as detailed in encapsulation efficiency section. Drug solubility was calculated from Beer-Lambert plots. In case of cinnarizine, drug concentration was assessed in saturated solution according to the HPLC method reported in the previous section.

***In vitro* drug release from microparticles**

The USP II paddle apparatus (Model PTWS, Pharmatest, Hainburg, Germany) equipped with inline analysis coupled with 0.22 μ m filter was employed to assess the microparticles' dissolution profiles. Microparticles (0.1g) were accurately weighed and filled into capsule size 0. Each capsule was placed in a metal sinker to ensure a submerged position in a vessel containing 750 mL of 0.1N HCl as dissolution medium at 37 ± 0.5 °C. After 120 min, 250 mL of 0.2M tri-sodium phosphate (equilibrated to 37 ± 0.5 °C) was added to the dissolution vessel, and the pH of the solution was adjusted to 7.4 ± 0.05 if necessary using 5N HCl or 4N NaOH solutions, and the dissolution experiment was continued for another 4 hours. Samples were taken every 5 min, the speed of the paddle was 100 rpm and each dissolution test was replicated 3 times. Data were processed using Icalis software (Icalis Data Systems Ltd, Berkshire, UK). A standard calibration curve was prepared for each drug in acidic and

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buffer media. The absorbance of blank microparticles following the same dissolution procedure was measured and subtracted from those of the drug loaded microparticles to remove any interference from the Eudragit polymer and gelatin capsules. In case of cinnarizine, HPLC method reported above was applied to medium solutions.

Multiple Regression

Standard multiple regression using SPSS statistics software 17.0.0 (SPSS Inc., Chicago, U.S.) was conducted to assess the feasibility of predicting the control of drug release from microparticles in acidic medium from the following variables: drug molecular weight and its solubility in acid and microparticle diameter. The highly spherical morphology of the microparticles and the narrow size distribution of the majority of the prepared particles allowed the use of the square of diameter as representative of particles surface area. No violation of the assumptions of normality, linearity, multicollinearity and homoscedasticity was found.

RESULTS AND DISCUSSION

Microsphere properties

All nine drugs were successfully encapsulated into Eudragit L and Eudragit S microparticles. The particles were spherical and had a uniform size distribution of 25-60 μm and 35-55 μm for Eudragit L and Eudragit S respectively (Table 1). Representative SEM images of amprenavir and prednisolone loaded microparticles are shown in Fig.1. According to the SEM images, there was no evidence of porosity in any of the fabricated microparticles. In addition, X-ray powder diffraction and thermal analysis showed no evidence of crystallinity in the microparticles.

Eudragit S microparticles were significantly larger than Eudragit L ones (paired samples t-test, $t(11)=3.39$, $p<0.01$). A greater size of Eudragit S microparticles prepared under the same conditions as Eudragit L microparticles was also reported by Kendall et al. (2009) and was attributed to the nature of polymers; the higher viscosity of Eudragit S solution leading to the formation of larger emulsion droplets under the same stirring conditions. The encapsulation efficiency was high for all drugs (60-90%, Table 1) with Eudragit S microparticles having slightly (but statistically significantly) higher encapsulation

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3 efficiencies than Eudragit L microparticles (paired samples t-test, $t(11)=5.76$, $p<0.0005$).
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5 The data shows the universal ability of this microparticle system to encapsulate drug
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7 molecules with a wide range of physicochemical properties.
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10 ***In vitro* drug release from microparticles**

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13 The release profiles of the nine drugs from Eudragit S and Eudragit L microparticles are
14 shown in Figs. 2 and 3 respectively. Release of dipyridamole, cinnarizine, amprenavir,
15 bendroflumethiazide, budenoside, prednisolone in acidic medium was well-controlled from
16 both Eudragit S and Eudragit L microparticles, being less than 10% of the total drug
17 content after 120 min. In contrast, the release of paracetamol, salicylic acid and ketoprofen
18 were poorly controlled (>10% of drug content).
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26 Upon changing the pH to 6.8 and 7.4 for Eudragit L and Eudragit S microparticles
27 respectively, rapid and complete drug release was achieved within 20 min and 45 min for
28 Eudragit L and Eudragit S respectively for all drugs except for cinnarizine (Figs. 2 and 3).
29 The slower release from Eudragit S microparticles could be due to its larger size (and hence
30 smaller surface area), as well as a slower dissolution of the Eudragit S polymer. A lower
31 dissolution rate of Eudragit S films (compared to Eudragit L ones) has been reported¹⁷. The
32 limited release of cinnarizine at high pH is attributed to the poor solubility of the basic drug
33 in phosphate buffer. It was noted that drug crystals appeared in the dissolution medium
34 after pH change, indicating a rapid precipitation of cinnarizine.
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44 **Influence of drug and particle properties on the control of drug release in acid** 45 **medium**

46 Plots of drug release versus: i) drug molecular weight, ii) solubility in acidic medium and
47 iii) microsphere size are shown in Figs. 4-6. No clear relationship was found between the
48 solubility of the drug in acid medium or microsphere size and drug release in the acidic
49 medium. In contrast, the drug's molecular weight seemed to have a significant impact on its
50 release, drug release decreasing exponentially with increasing molecular weight. A
51 minimum molecular weight of around 300 Da seems to be necessary for control of drug
52 release in acid medium (Fig. 6). A larger molecular size of the drug is likely to impede its
53 movement through the polymeric network of the microparticle matrix and hence its release
54 in acid medium⁷. The relative importance of the two drug properties, molecular weight and
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3 drug acid solubility, can be visualised in Figs. 7a-b. The figures clearly illustrate that
4 release of larger drug molecules (>300 Da) are likely to be well-controlled and fulfil the
5 USP criteria for delayed release formulations regardless of the drug's solubility in the
6 medium.
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12 To quantify the different influences, multi-linear regression was conducted, and yielded the
13 following equation:
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17 Drug Released (%) =

$$55.123 - 0.123 \text{ MW} + 9.7 \text{ Log (Sol)} - 0.012 d^2 + 1.55 P$$

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20 Eq.5

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22 where MW = drug molecular weight (Da), Log(Sol) = logarithm of drug saturation
23 solubility in the acidic medium at 37 °C assessed in mg/L, d = Median diameter of
24 microparticles (μm) and P is a constant relating to the polymer, P = 0 for Eudragit S and P
25 = 1 for Eudragit L.
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32 It can be seen that drug release was increased by higher drug solubility and reduced by
33 higher drug molecular weight and larger microparticle size. The multiple regression
34 standardized coefficients revealed that molecular weight was by far the most prominent
35 factor in controlling drug release (Standardized coefficient Beta = -0.617, $p < 0.001$) while
36 drug solubility (Beta = 0.403, $p < 0.01$) and microsphere size (Beta = -0.396, $p < 0.05$) had
37 smaller influences. The model also suggests that the nature of polymethacrylate polymer
38 (Eudragit S or Eudragit L) has no significant effect in controlling drug release in the acidic
39 medium (Beta = 0.03, $p = 0.79$). According to the model, replacing Eudragit S with Eudragit
40 L was expected to increase drug release after two hours in the acid by less than 2%.
41 Equation 5 was able to describe 84 % of the total variance ($F(4, 17) = 22.111$, $p < 0.0005$).
42 Other factors not investigated in this study are also expected to affect drug release from
43 polymeric matrix systems such as drug-polymer interactions¹⁸⁻²¹.
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54 55 CONCLUSIONS

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58 Nine drugs with different chemical natures were encapsulated in Eudragit L and Eudragit S
59 microparticles using a novel emulsion solvent evaporation method. This showed the
60 universality of the employed method for the preparation of delayed release particulate

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3 formulations. The particles had the desirable properties of spherical morphology, smooth
4 surface, small microsphere size ($<100\mu\text{m}$) and a uniform size distribution. However, all the
5 drug-loaded microparticles did not conform to USP specifications with respect to control of
6 drug release in acid medium for delayed release preparations i.e. release of $<10\%$ of drug
7 content following a 2 hour incubation in an acid medium. Paracetamol, ketoprofen and
8 salicylic acid were released at $>10\%$. When the influences of the drug's molecular weight,
9 acid solubility and microsphere size on drug release in acid medium were modelled using
10 multiple regression, the drug molecular weight was found to be the most important
11 predictor while the drug's acid solubility and the microsphere size were less influential.
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List of figures

Fig. 1. SEM micrograph of amprenavir (1a and 1b), prednisolone (1c and 1d) loaded Eudragit S and Eudragit L microparticles

Fig. 2. % drug release from Eudragit L microparticles with time, using a pH-change dissolution method.

Fig. 3. % drug release from Eudragit S microparticles with time, using a pH-change dissolution method.

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3 Fig. 4. % drug release from microparticles as a function of drug acid solubility (the dotted
4 line represents USP criteria)
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9 Fig. 5. % drug release from microparticles as a function of microsphere size (the dotted line
10 represents USP criteria)
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14 Fig. 6. % drug release from microparticles as a function of drug molecular weight (the
15 dotted line represents USP criteria)
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19 Fig. 7. Relative importance of drug molecular weight and drug acid solubility on drug
20 release from (a) Eudragit S and (b) Eudragit L microparticles after 2 hours in gastric
21 medium (sphere size is proportional to drug molecular weight, the dotted line represents
22 USP criteria).
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26 27 28 **List of tables**

29
30 Table 1: Drug's molecular weight and microsphere size, encapsulation efficiency and
31 percentage drug release in acid medium from Eudragit S and Eudragit L microparticles.
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Table 1

Drug	Solubility in acidic medium (mg/L)	Molecular weight (Da)	Particle size D(0,5)±SD µm (Span ±S.D)		Encapsulation efficiency (%) ±SD		Drug release after 2hours (%)±SD	
			Eudragit S	Eudragit L	Eudragit S	Eudragit L	Eudragit S	Eudragit L
Salicylic acid	1,435.5	138.1	46 ± 4.2 (3.0 ± 4.0)	31 ± 1.3 (0.7 ± 0.0)	107.2 ± 5.1	104 ± 1.9	40.8 ± 0.5	86.9 ± 1.3
Paracetamol	12,309	151.1	38 ± 1.9 (0.8 ± 0.07)	30 ± 1.2 (1.2 ± 0.1)	83.5 ± 0.7	83 ± 1.0	57.3 ± 0.3	63.2 ± 0.4
Ketoprofen	75.6	254.2	36 ± 1.2 (0.9 ± 0.3)	28 ± 0.9 (0.9 ± 0.1)	91.1 ± 1.1	90 ± 0.9	6.9 ± 0.8	17.1 ± 2.9
Prednisolone	218	360.4	48 ± 1.6 (0.6 ± 0.4)	38 ± 0.5 (0.7 ± 0.2)	80 ± 3.2	77 ± 1.2	1.6 ± 0.3	7.1 ± 0.3
Cinnarizine	2,110.6	369.5	49 ± 2.4 (0.7 ± 0.1)	56 ± 6.8 (1.2 ± 0.3)	64 ± 2.7	62 ± 1.9	0.0 ± 0.0	1.5 ± 0.2
Bendroflumethiazide	30.2	421.4	46 ± 13.5 (1.0 ± 0.1)	41 ± 4.1 (1.0 ± 0.1)	68 ± 0.9	63 ± 1.0	1.6 ± 0.3	3.1 ± 0.1
Budenoside	20.0	430.5	44 ± 1.6 (1.0 ± 0.2)	33 ± 0.5 (0.7 ± 0.1)	59 ± 5.7	53 ± 1.6	1.7 ± 0.8	3.4 ± 0.0
Dipyridamole	29,200	504.7	56 ± 0.2 (0.8 ± 0.1)	60 ± 5.9 (0.9 ± 0.1)	75 ± 1.7	70 ± 0.8	0.5 ± 0.4	0.0 ± 0.0
Amprenavir	89.0	505.6	36 ± 0.2 (0.9 ± 0.1)	27 ± 1.1 (0.9 ± 0.2)	68 ± 3.1	60 ± 0.8	0.0 ± 0.0	0.0 ± 0.0

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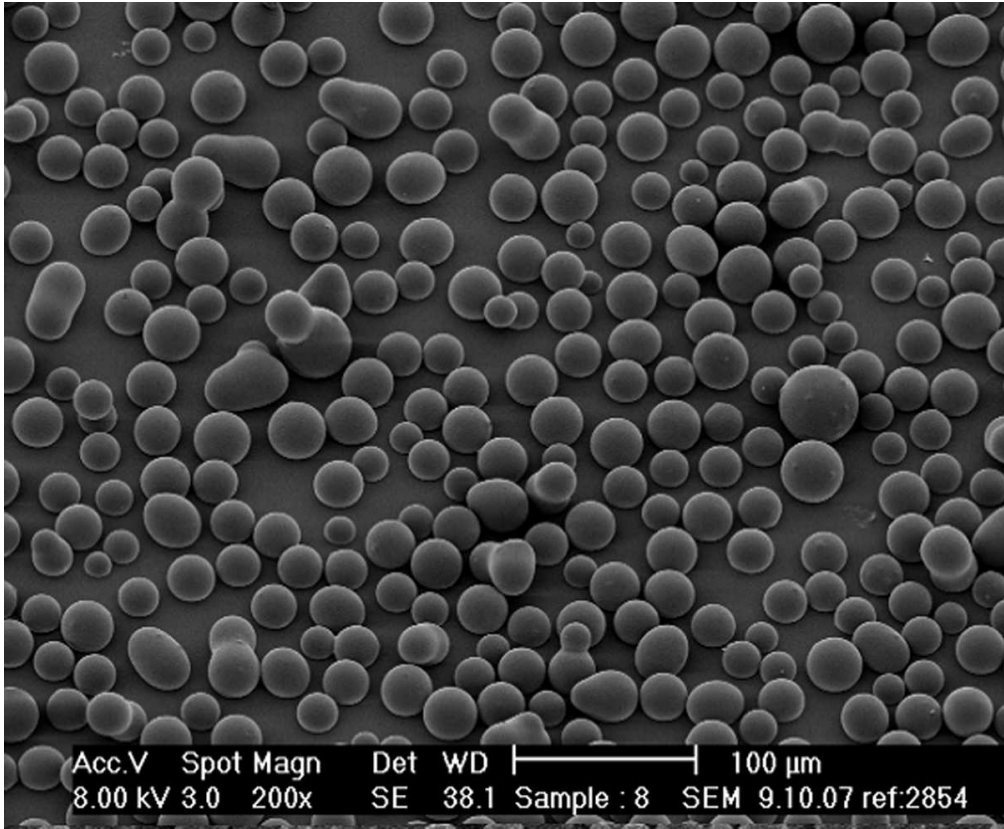
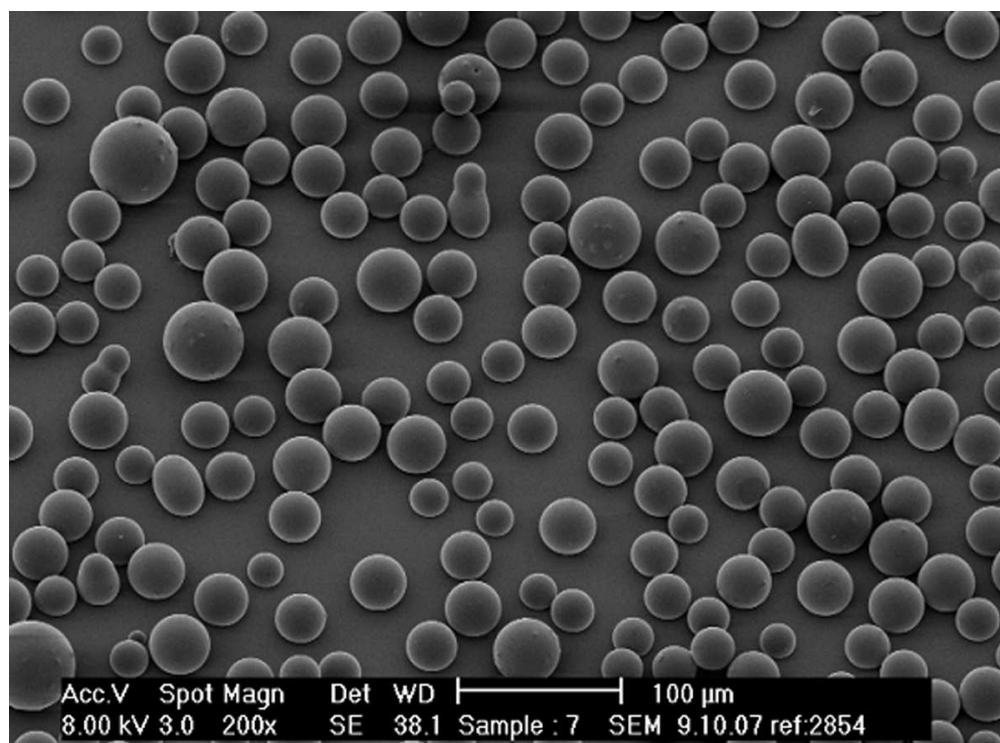


Figure 1a
423x350mm (72 x 72 DPI)

view



33 Figure 1b
34 423x311mm (72 x 72 DPI)

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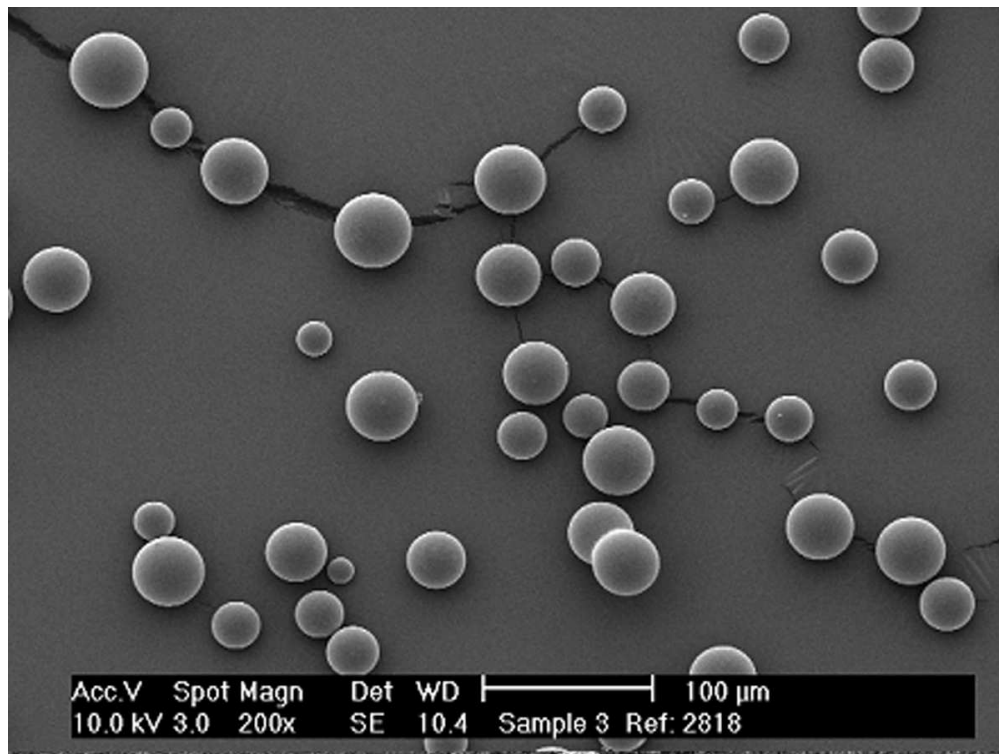
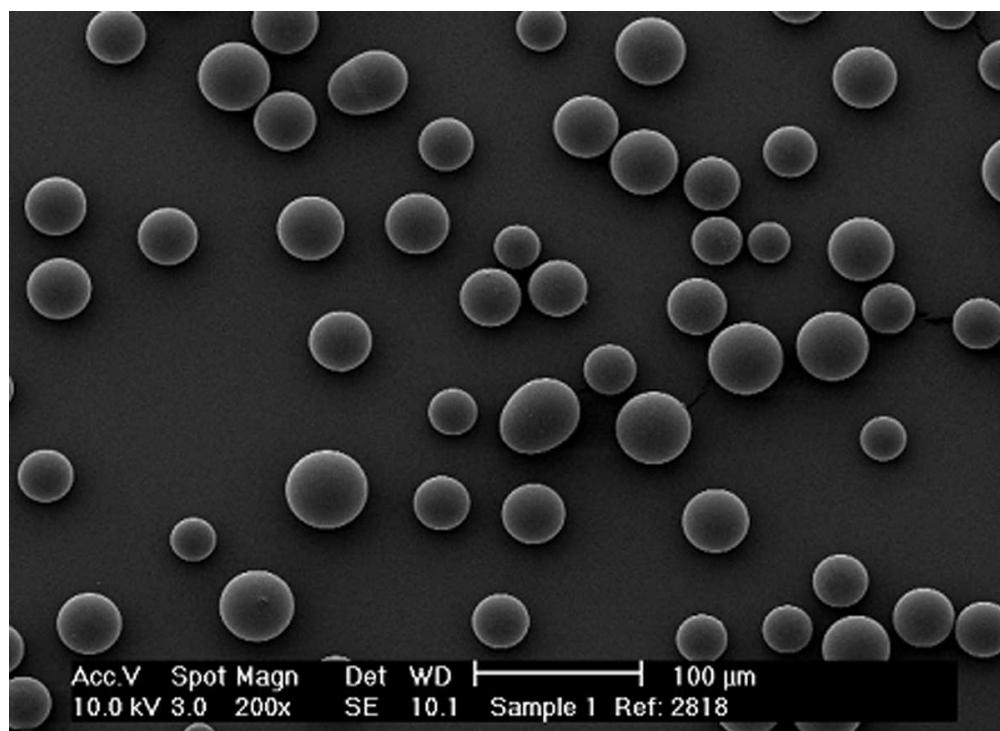


Figure 1c
423x316mm (72 x 72 DPI)

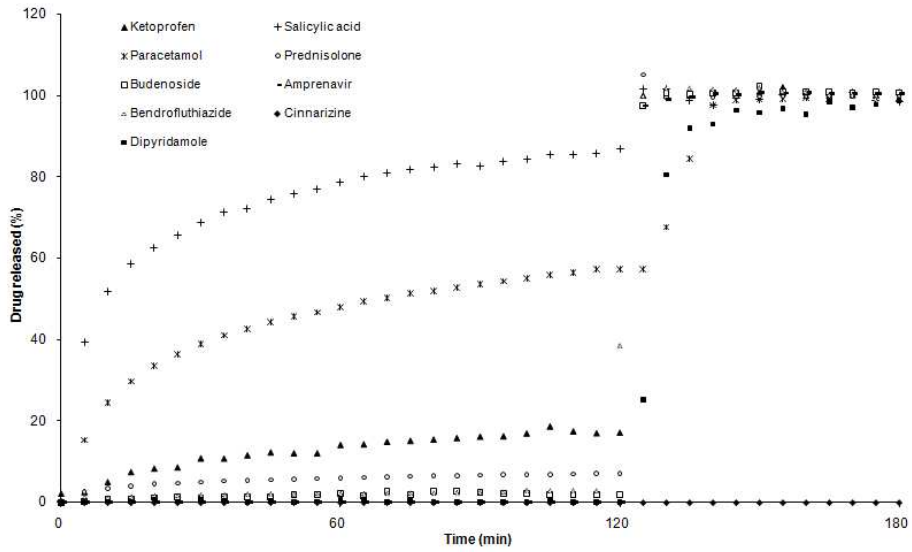
Review



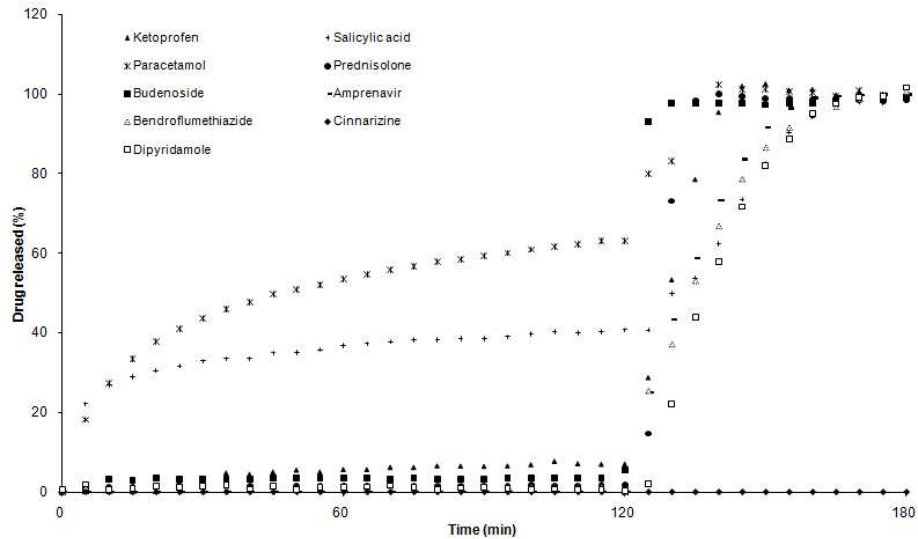
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Figure 1d
423x306mm (72 x 72 DPI)

Review

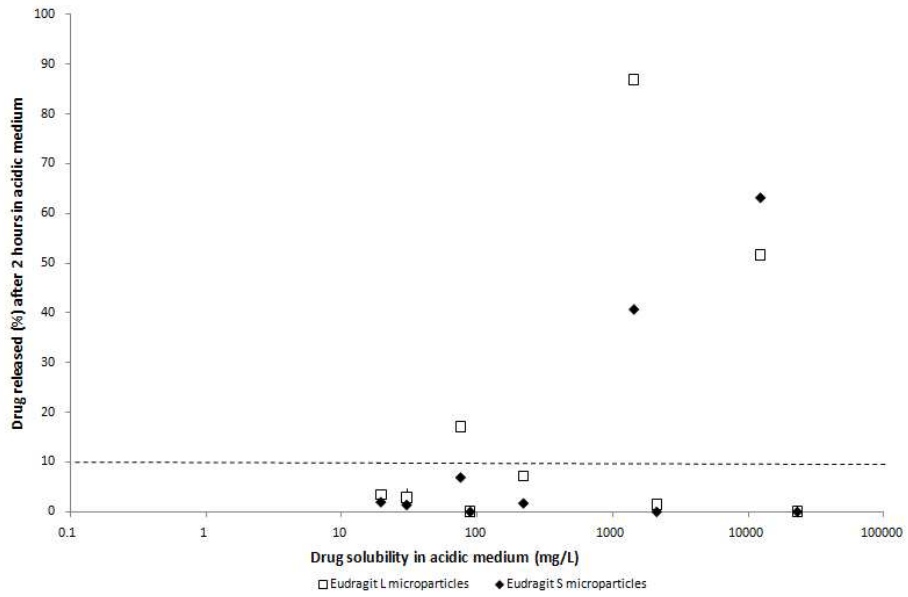


% drug release from Eudragit L microparticles with time, using a pH-change dissolution method
230x143mm (96 x 96 DPI)



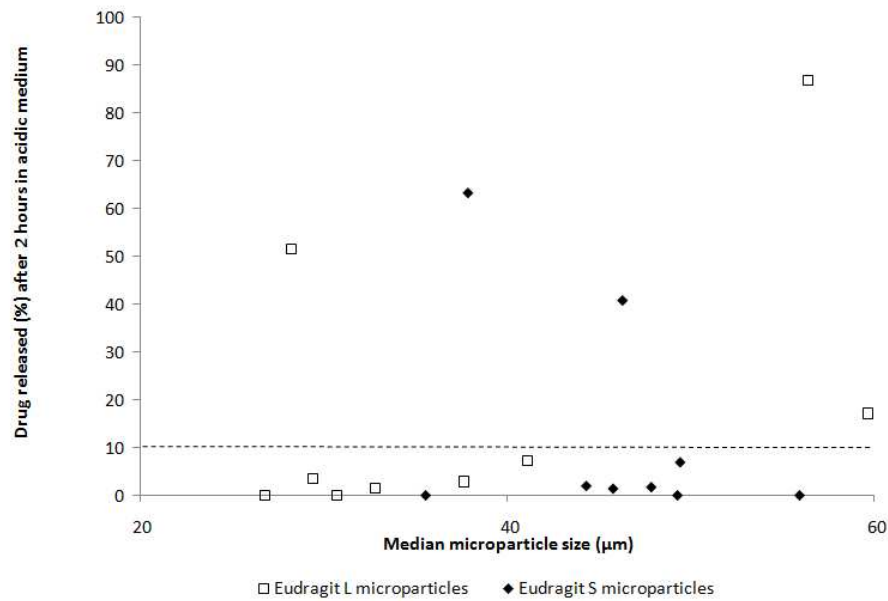
% drug release from Eudragit S microparticles with time, using a pH-change dissolution method
228x141mm (96 x 96 DPI)

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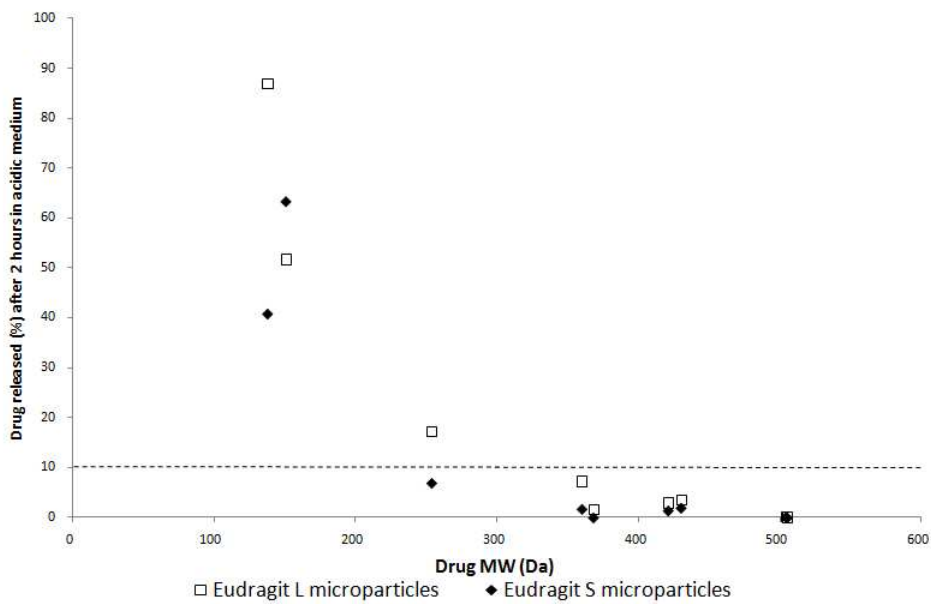


% drug release from microparticles as a function of drug acid solubility (the dotted line represents USP criteria)
228x141mm (96 x 96 DPI)

Review

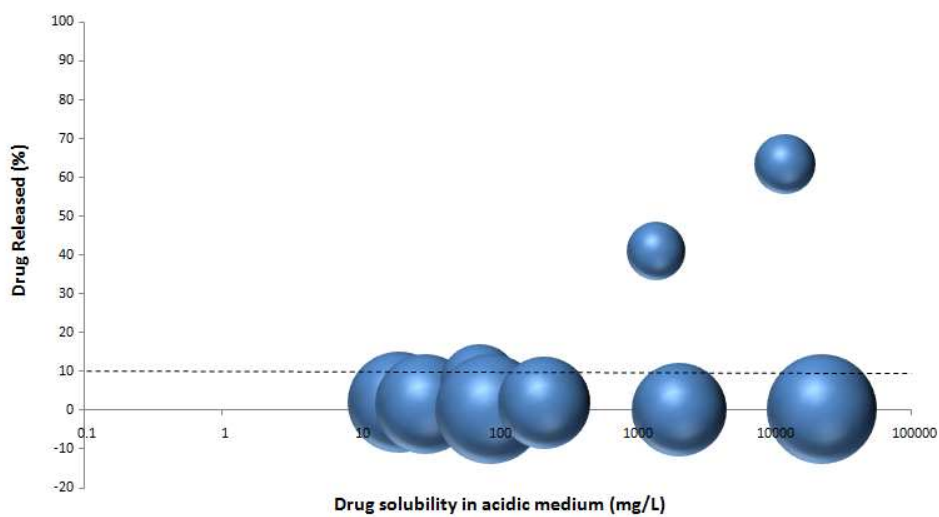


% drug release from microparticles as a function of microsphere size (the dotted line represents USP criteria)
220x143mm (96 x 96 DPI)

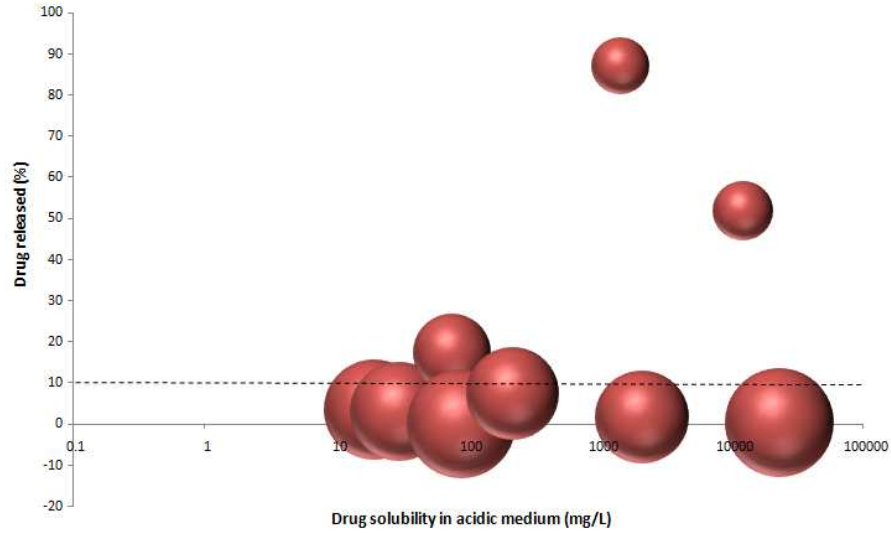


% drug release from microparticles as a function of drug molecular weight (the dotted line represents USP criteria)
 220x140mm (96 x 96 DPI)

Review



Relative importance of drug molecular weight and drug acid solubility on drug release from (a) Eudragit S and (b) Eudragit L microparticles after 2 hours in gastric medium (sphere size is proportional to drug molecular weight, the dotted line represents USP criteria)
211x127mm (96 x 96 DPI)



Relative importance of drug molecular weight and drug acid solubility on drug release from (a) Eudragit S and (b) Eudragit L microparticles after 2 hours in gastric medium (sphere size is proportional to drug molecular weight, the dotted line represents USP criteria).
213x126mm (96 x 96 DPI)

Review