SPRAY DRIED POWDERS FOR USE IN
DRY POWDER AEROSOL FORMULATION

By
Aneeta Chawla

The School of Pharmacy
University of London
January 1993

Thesis Submitted for the degree of Doctor of Philosophy in the University of London
Dedication

To my parents and my brother.
With all my love
Abstract

Spray Dried Powders for Use in Dry Powder Aerosol Formulation

Spray drying was employed as a means of controlled particle size reduction of powders, for use in formulation of therapeutic dry powder aerosols. Spray drying is a process whereby a solution, slurry or suspension is atomised into a fine spray, mixed with warmed air and allowed to evaporate to a dry particulate powder. It has been used successfully by many industries, including the pharmaceutical industry, to produce products of well defined physical and chemical properties. It has the advantage of being a simple one stage process, for which the operation variables can be accurately controlled and if necessary fully automated.

The drugs; isoprenaline sulphate and hydrochloride, salbutamol base and sulphate and pentamidine isethionate were preliminarily investigated, from which salbutamol sulphate was chosen as a model drug for further studies. The spray drying process was optimised, in terms of particle size and percentage yield, for salbutamol sulphate using 2^4 factorial design analysis, investigating the pump speed, aspirator level, heat control level and feed concentration.

Physical properties, important for dry powder aerosol formulation, of spray dried salbutamol sulphate, were investigated and compared to those of the micronised drug usually used in this type of formulation. The properties investigated were as follows: powder flow expressed in terms of flow parameters such as angle of repose, angle of spatula, compressibility (Carr’s compressibility ratio) and cohesion/uniformity; particle size, measured by scanning microscopy, computer image analysis and laser diffraction; size distribution, measured by laser diffraction; shape, evaluated using computer image analysis; apparent density, measured using an air comparison pycnometer, crystallinity, evaluated by x-ray diffraction and in vitro lung deposition, evaluated using the twin impinger and cascade impactor apparatus.

Spray drying was seen to produce spherical, amorphous particles of narrow size distribution suitable for inhalation, that is below 10 μm. Spray drying did not alter the chemical nature, determined by infra red spectroscopy or affect substantially drug potency, determined by fluorospectroscopy. It did however alter the crystallinity, shown by x-ray diffraction.

The surface energies of both spray dried and micronised salbutamol sulphate forms, together with lactose, medium grade and spray dried, were calculated from contact angle measurements, made using the Wilhelmy gravitational method. These were then used in the determination of polarity, work of adhesion, work of cohesion and spreading coefficients of the materials. The results of which were discussed in connection with powder properties of flow and in vitro deposition. This preliminary work showed, within the limitations of the experimentation, surface energy, work of adhesion, work of cohesion and spreading coefficient to have potential in the prediction of powder behaviour and interaction of powders, in dry powder aerosol formulation, including the liberation of the drug from inert carriers.
Acknowledgements

Few things are done in isolation and my thesis could not have been written without the help and encouragement of the following, to whom I will always be grateful.

Thanks are due to my supervisors, Dr Kevin Taylor and Professor J M Newton. Without their endless support and encouragement I would still be at the starting post. The Staff of the Pharmaceutics Department. Kurt and Graham of the computer unit, for their persuasion, albeit not so gentle, to complete (and free one of their computers). Dave MacCarthy of the Electron Microscopy Unit for all his help and bad jokes. Graham Buckton for his help and advice with the surface energetic research. The staff at Rhône-Poulenc Rorer Ltd., the Research and Development Division, especially Dr Gordon Simpkin, for all their practical advice and support.

A special thanks must go to all my friends, whom over the last three years have provided encouragement and endless humour when it was most needed.

The project could not have been undertaken without funding from Dr M Johnson of Rhône-Poulenc Rorer Ltd. and the Science and Engineering Research Council.
Contents

Dedication 2
Abstract 3
Acknowledgements 4
List of Figures 10
List of Tables 15
List of Plates 21

Chapter 1

Introduction 23

1.1 Pulmonary Drug Delivery 24
1.2 Anatomy and Physiology of the Respiratory Tract 25
1.3 Drug Deposition in the Lung 27
1.4 Aerosol Formulation 33
  1.4.1 Metered Dose Inhalers 33
  1.4.2 Dry Powder Inhalers 38
1.5 Controlled Particle Size Preparation 44
1.6 Research Aims 47

Chapter 2

Spray Drying 48

2.1 Introduction 49
2.1.1 Spray Drying Operation 49
  2.1.1.1 Atomisation 50
  2.1.1.2 Spray Gas Contact 52
  2.1.1.3 Drying 54
  2.1.1.4 Product Separation and Recovery 59

2.1.2 Effect of Spray Drying Variables on the Product 60

2.1.3 Advantages and Disadvantages of Spray Drying 62

2.2 Materials and Methods 64
  2.2.1 Materials 64
  2.2.2 Spray Drying 65
  2.2.3 Measurement of Yield 70
  2.2.4 Particle Size Measurement 70
  2.2.5 Photography of Atomised Spray 74

2.3 Results 76
  2.3.1 Scanning Electron Microscopy 76
  2.3.2 Particle Sizing Using Laser Diffraction 76
  2.3.3 Spray Drying Results 84
  2.3.4 Photography of the Atomised Spray 107

2.4 Discussion 113

2.5 Conclusions 115

Chapter 3

Factorial Design Analysis 117

3.1 Introduction 118
3.2 Methods

3.3 Results and Statistical Analysis

3.3.1 Results

3.3.1.1 Particle Size Data

3.3.1.2 Percentage Yield Data

3.3.2 Statistical Analysis of $2^4$ Factorial Experimental Design

3.4 Conclusions

Chapter 4

Physico-Chemical Analysis

4.1 Introduction

4.1.1 In Vitro Deposition Measurements

4.1.2 Powder Flow

4.1.2.1 Properties Affecting Powder Flow

4.1.2.2 Measurement of Powder Flow

4.2 Materials and Methods

4.2.1 Materials

4.2.2 Spray Drying

4.2.3 Particle Size, Size Distribution and Shape

4.2.4 Specific Surface Area

4.2.5 Density Measurement

4.2.6 Hollowness of Spray Dried Particles

4.2.7 X-Ray Diffraction
Chapter 5

Surface Energetics

5.1 Introduction

5.1.1 Contact Angle Measurement
5.1.2 Calculation of Surface Energy 215
5.1.3 Calculation of Other Parameters 221

5.2 Materials and Methods 223
5.2.1 Materials 223
5.2.2 Methods 224

5.3 Results and Discussion 228
5.3.1 Contact Angle Measurements 228
5.3.2 Calculation of Surface Energy 231
5.3.3 Calculation of Work of Cohesion, Work of Adhesion and Spreading Coefficients 237

5.4 Conclusions 241

Chapter 6
Summary and Further Work 242

6.1 Summary 243
6.2 Further Work 247

Appendices 250
Appendix 1 251
Appendix 2 252
Appendix 3 254
Appendix 4 256

References 257
List of Figures

1.1 Human Respiratory Tract (Schematic Diagram). 26
1.2 Schematic Diagram of Particle Deposition in the Lung. 31
1.3 Plot Showing Fractional Particle Deposition in the Respiratory Tract. 32
1.4 Metered Dose Inhaler, Showing the Metering Valve Mechanism. 35
1.5 The Spinhaler® Device (Fisons). 41
1.6 The Rotahaler® Device (Glaxo). 42
1.7 The Turbohaler® Device (Astra). 43
1.8 Fluid Energy Mill. 45
2.1 Pneumatic Nozzle Mechanism. 52
2.2 A Graphical Relationship between Drying Rate and Moisture Content (adapted from Masters, 1990). 55
2.3 A Graphical Relationship between Temperature and Moisture Content in During the Drying Process (Adapted from Masters, 1990). 56
2.4 Büchi 190 Mini Spray Dryer. 68
2.5 Flow Diagram of the Spray Drying Process. 69
2.6 Stub Positions Investigated in Spray Dryer Collection Vessel. 70
List of Figures Contd.

2.7 Phillips XL20, Scanning Electron Microscope. 72
2.8 Apparatus for Photographing Atomised Spray from the Spray Dryer Nozzle. 75
2.9 The Effect of Temperature Control Level on Percentage Yield of Spray Dried Isoprenaline Sulphate. 91
2.10 The Effect of Pump Speed on the Percentage Yield of Spray Dried Isoprenaline Sulphate. 91
2.11 The Effect of Pump Rate on the Median Particle Size of Spray Dried Isoprenaline Sulphate. 92
2.12 The Effect of Spray Flow (Quantity of Pressurised Air) on the Percentage Yield of Isoprenaline Sulphate. 92
2.13 The Effect of Feed Concentration on the Percentage Yield of Spray Dried Isoprenaline Sulphate. 93
2.14 The Effect of Feed Concentration on the Median Particle Size of Spray Dried Isoprenaline Sulphate. 93
2.15 The Effect of Heating Control Level on the Particle Size of Spray Dried Salbutamol Sulphate at Different Feed Concentrations. 105
2.16 The Effect of Heating Control Level on the Percentage Yield of Spray Dried Salbutamol Sulphate at Different Feed Concentrations. 105
4.1 Twin Impinger. 134
4.2 Anderson Mark II Cascade Impactor. 137
<table>
<thead>
<tr>
<th>Figure</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.3</td>
<td>Air Flow Pattern Through Cascade Impactor.</td>
</tr>
<tr>
<td>4.4</td>
<td>Beckman 930, Air Comparison Pycnometer, Schematic Diagram.</td>
</tr>
<tr>
<td>4.5</td>
<td>Hosokawa, Powder Characteristic Tester.</td>
</tr>
<tr>
<td>4.6</td>
<td>Angle of Repose Measurement.</td>
</tr>
<tr>
<td>4.7</td>
<td>Angle of Spatula Measurement.</td>
</tr>
<tr>
<td>4.8</td>
<td>Sampling Positions for Mixing Experiment.</td>
</tr>
<tr>
<td>4.9</td>
<td>Size Distribution of Spray Dried Salbutamol Sulphate Measured by Laser Diffraction.</td>
</tr>
<tr>
<td>4.10</td>
<td>Cumulative Undersize/Oversize and Frequency Plot for Spray Dried Salbutamol Sulphate.</td>
</tr>
<tr>
<td>4.11</td>
<td>Size Distribution of Micronised Salbutamol Sulphate Measured by Laser Diffraction.</td>
</tr>
<tr>
<td>4.12</td>
<td>Cumulative Undersize/Oversize and Frequency Plot for Micronised Salbutamol Sulphate.</td>
</tr>
<tr>
<td>4.13</td>
<td>Image Created by Image Analyser.</td>
</tr>
<tr>
<td>4.14</td>
<td>Scatter Plot Indicating Shape of a Spray Dried Salbutamol Sulphate Particle.</td>
</tr>
<tr>
<td>4.15</td>
<td>Scatter Plot Indicating Shape of a Micronised Salbutamol Sulphate Particle.</td>
</tr>
<tr>
<td>4.16</td>
<td>X-Ray Diffraction Profiles of Micronised Salbutamol Sulphate (b) Spray Dried Salbutamol Sulphate.</td>
</tr>
</tbody>
</table>
List of Figures Contd.

4.17 DSC Thermograms Showing for (a) Spray Dried and (b) Micronised Salbutamol Sulphate. 176

4.18 DSC Thermogram Showing Peak Analysis for Spray Dried Salbutamol Sulphate. 177

4.19 DSC Thermogram Showing Peak Analysis for Micronised Salbutamol Sulphate. 178

4.20 DSC Thermogram for Two Different Batches of Micronised Salbutamol Sulphate. 179

4.21 IR Spectrum for Salbutamol Sulphate (BP Reference Spectrum). 180

4.22 IR Spectrum for Spray Dried Salbutamol Sulphate. 181

4.23 IR Spectrum for Micronised Salbutamol Sulphate. 181

4.24 The Influence of Spray Dried and Micronised Salbutamol Sulphate on the Flowability Index of Avicel. 190

4.25 The Influence of Spray Dried and Micronised Salbutamol Sulphate on the Flowability Index of Medium Grade Lactose. 190

4.26 UV Absorbance Spectrum for Lactose. 192

4.27 The Effect of Lactose Concentration on UV Absorbance of a 0.01% Solution of Salbutamol Sulphate. 193

4.28 The Effect of Mixing Time on Salbutamol Sulphate/Lactose Mix (a) 90 r.p.m (b) 42 r.p.m. 193
## List of Figures Contd.

5.1 Wilhelmy Apparatus (Schematic Diagram). 213
5.2 Typical Force as a Function of Depth Immersion Plot using Wilhelmy Gravitational Method. 213
5.3 Stainless Steel Punch and Die Assembly and Press. 226
List of Tables

2.1 Spray Drying Conditions Investigated for Isoprenaline Hydrochloride. 65
2.2 Spray Drying Conditions Investigated for Isoprenaline Sulphate. 66
2.3 Spray Drying Conditions Investigated for Salbutamol Base. 66
2.4 Spray Drying Conditions Investigated for Salbutamol Sulphate. 67
2.5 Spray Drying Conditions Investigated for Pentamidine Isethionate. 67
2.6 The Effect of Time on the Median Particle Size of Spray Dried Salbutamol Base, Dispersed in Cyclohexane. 77
2.7 Tables (a-g). The Effect of stirring time on the Median Particle Size of Spray Dried Salbutamol Base, Dispersed in Cyclohexane. 78
2.8 Tables (a-e). The effect of Sonication time on the Measured Median Particle Size of Spray Dried Salbutamol Base, Dispersed in Cyclohexane. 81
2.9 Median Particle Size of Spray Dried Isoprenaline Sulphate as a Function of Time. Sample Sonicated for a Few Seconds Before Sizing. 83
2.10 Spray Drying of Isoprenaline Hydrochloride. 85
<table>
<thead>
<tr>
<th>Table</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.11</td>
<td>The Effect of Heating Control Level on Spray Drying of Isoprenaline Sulphate.</td>
<td>87</td>
</tr>
<tr>
<td>2.12</td>
<td>The Effect of Pump Rate on the Spray Drying of Isoprenaline Sulphate.</td>
<td>88</td>
</tr>
<tr>
<td>2.13</td>
<td>The Effect of the Aspirator Level on the Spray Drying of Isoprenaline Sulphate.</td>
<td>88</td>
</tr>
<tr>
<td>2.14</td>
<td>The Effect of Feed Concentration on Spray Drying of Isoprenaline Sulphate.</td>
<td>89</td>
</tr>
<tr>
<td>2.15</td>
<td>The Effect of Spray Flow Rate (Quantity of Pressurised Air) on Spray Drying of Isoprenaline Sulphate.</td>
<td>90</td>
</tr>
<tr>
<td>2.16</td>
<td>The Effect of the Heating Control Level on Spray Drying of Salbutamol Base.</td>
<td>96</td>
</tr>
<tr>
<td>2.17</td>
<td>The Effect of Pump Rate on Spray Drying of Salbutamol Base.</td>
<td>97</td>
</tr>
<tr>
<td>2.18</td>
<td>The Effect of Aspirator Level on Spray Drying of Salbutamol Base.</td>
<td>98</td>
</tr>
<tr>
<td>2.19</td>
<td>The Effect of Feed Concentration on Spray Drying of Salbutamol Base.</td>
<td>99</td>
</tr>
<tr>
<td>2.20</td>
<td>The Effect of Heating Control Level on Spray Drying of Salbutamol Sulphate.</td>
<td>102</td>
</tr>
<tr>
<td>2.21</td>
<td>The Effect of Aspirator Level on Spray Drying of Salbutamol Sulphate.</td>
<td>103</td>
</tr>
</tbody>
</table>
## List of Tables Contd.

<table>
<thead>
<tr>
<th>No.</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.22</td>
<td>The Effect of Feed Concentration on Spray Drying of Salbutamol Sulphate.</td>
<td>104</td>
</tr>
<tr>
<td>2.23</td>
<td>The Effect of the Heat Control Level on Spray Drying of Pentamidine Isethionate.</td>
<td>109</td>
</tr>
<tr>
<td>2.24</td>
<td>The Effect of the Aspirator Level on Spray Drying of Pentamidine Isethionate.</td>
<td>110</td>
</tr>
<tr>
<td>2.25</td>
<td>The Effect of Feed Concentration on Spray Drying of Pentamidine Isethionate.</td>
<td>111</td>
</tr>
<tr>
<td>2.26</td>
<td>The Most Suitable Spray Drying Conditions for Isoprenaline Sulphate, Salbutamol Base and Salbutamol Sulphate.</td>
<td>116</td>
</tr>
<tr>
<td>3.1</td>
<td>Factors and the Levels used in the Experimental Factorial Design.</td>
<td>119</td>
</tr>
<tr>
<td>3.2</td>
<td>Particle Size Results for Experimental Factorial Design.</td>
<td>121</td>
</tr>
<tr>
<td>3.3</td>
<td>Percentage Yield Results for Experimental Factorial Design.</td>
<td>122</td>
</tr>
<tr>
<td>3.4</td>
<td>Contrast Constants for the $2^4$ Factorial Design.</td>
<td>124</td>
</tr>
<tr>
<td>3.5</td>
<td>Calculation of the Degrees of Freedom in Factorial Design Analysis.</td>
<td>126</td>
</tr>
<tr>
<td>3.6</td>
<td>Results from the Analysis of Variance, using Particle Size Data.</td>
<td>128</td>
</tr>
</tbody>
</table>
List of Tables Contd.

3.7 Results From the Analysis of Variance, using Percentage Yield Data. 130

4.1 Flowability Index Values. 159

4.2 Particle Size Analysis of Spray Dried and Micronised Salbutamol Sulphate Using Laser Diffraction. 166

4.3 Size Analysis of Spray Dried Salbutamol Sulphate Particles (823) using the Image Analyser. 166

4.4 Shape Analysis Using the Image Analyser. 170

4.5 Density Measurements. 171

4.6 Powder Flow Characteristics of Avicel/Aerosil Mixes. 184

4.7 Powder Flow Characteristics of Avicel/Spray Dried Salbutamol Sulphate Mixes. 185

4.8 Powder Flow Characteristics of Avicel/Micronised Salbutamol Sulphate Mixes. 186

4.9 Powder Flow Characteristics of Lactose/Spray Dried Salbutamol Sulphate Mixes. 187

4.10 Powder Flow Characteristics of Lactose/Micronised Salbutamol Sulphate. 188

4.11 Powder Flow Characteristics of Spray Dried and Micronised Salbutamol Sulphate. 189

4.12 Uniformity of Capsule Content (unsieved powder). 194

4.13 Uniformity of Capsule Content (sieved powder). 194
List of Tables Contd.

4.14 Twin Impinger Analysis of Spray Dried and Micronised Salbutamol Sulphate Liberated from the Rotahaler®. 196

4.15 Twin Impinger Analysis of Spray Dried and Micronised Salbutamol Sulphate Liberated from the Spinhaler®. 196

4.16 Stage II Twin Impinger Analysis of Drug with Carrier, Liberated From a Rotahaler®. 197


4.18 Cascade Impactor Analysis of Spray Dried Salbutamol Sulphate Delivered from the Rotahaler®. 201

4.19 Cascade Impactor Analysis of Micronised Salbutamol Sulphate Delivered from the Rotahaler®. 202

4.20 Cascade Impactor Analysis of a Proprietary Brand of Salbutamol Sulphate (Ventolin Rotacaps®) Delivered from the Rotahaler®. 203

4.21 Mass Mean Aerodynamic Diameters, from Cascade Impactor Analysis. 204

5.1 Literature Surface Energies for Test Liquids used in Contact Angle Measurements. 228

5.2 Contact Angle Measurements (advancing angle) using Spray Dried Salbutamol Sulphate. 229
5.3 Contact Angle (advancing angle) Measurements using Micronised Salbutamol Sulphate. 229

5.4 Contact Angle Measurements (advancing angle) for Spray Dried and Medium Grade Lactose using Propylene Glycol and Glycerol Test Liquids. 230

5.5 Calculated Surface Energies (mNm\(^{-1}\)) for Spray Dried Salbutamol Sulphate. 233

5.6 Calculated Surface Energies (mNm\(^{-1}\)) for Micronised Salbutamol Sulphate. 234

5.7 Calculated Surface Energies (mNm\(^{-1}\)) for Spray Dried and Medium Grade Lactose. 236

5.8 Surface Energies and Components (mNm\(^{-1}\)) used to Calculate Work of Cohesion, Work of Adhesion and Spreading Coefficients. 237

5.9 Calculated Works of Cohesion. 238

5.10 Works of Adhesion between Salbutamol Sulphate and Lactose Powders. 238

5.11 Spreading Coefficients (\(\lambda_{12}\) and \(\lambda_{21}\)) for Salbutamol Sulphate and Lactose Powders. 240
List of Plates

2.1 Isoprenaline Sulphate Starting Material. 86
2.2 Isoprenaline Sulphate, Spray Dried Material. 86
2.3 Salbutamol Base, Starting Material. 95
2.4 Salbutamol Base, Spray Dried Material. 95
2.5 Salbutamol Sulphate, Starting Material. 101
2.6 Salbutamol Sulphate, Spray Dried Material. 101
2.7 Pentamidine Isethionate, Starting Material. 106
2.8 Pentamidine Isethionate, Spray Dried Material. 106
2.9 Pentamidine Isethionate, Spray Dried Material (Lot Pen 9). 108
2.10 Photograph of the Atomised Spray as it Emerges from the Spray Dryer Atomiser. 112
4.1 Particle of Micronised Salbutamol Sulphate Assigned for Shape analysis. 168
4.2 Particle of Spray Dried Salbutamol Sulphate Assigned for Shape Analysis. 168
4.3 TEM Showing Spray Dried Salbutamol Sulphate (200KV). 173
4.4 TEM, Showing Freeze Fracture Replicates of Spray Dried Salbutamol Sulphate. 173
5.1 Surface of Spray Dried Salbutamol Sulphate Compact Prepared using 1 Ton Pressure. 232
List of Plates Contd.

5.2 Surface of Spray Dried Salbutamol Sulphate Compact
Prepared using 2 Tons Pressure. 232

5.3 Surface of Spray Dried Salbutamol Sulphate Compact
Prepared using 3 Tons Pressure. 232

6.1 Co-Spray Dried Salbutamol Sulphate and Lactose. 248
Chapter One
Introduction
Introduction

1.1 Pulmonary Drug Delivery

Aerosols, as a means of drug delivery to the lung are well established and date back as far as the ancient civilisations, (Newman and Clarke, 1983). In the case of lung disorders aerosols have the advantage of site specific delivery, for example, the delivery of $\beta_2$-agonists in the treatment of bronchial asthma. Similarly delivery of corticosteroids, e.g. beclomethasone; bronchodilators, e.g. isoprenaline and mast cell stabilisers e.g. sodium cromoglycate (SCG), have been delivered by this method. Aerosols have also been used in the control of infection in cystic fibrosis, e.g. gentamicin and colistin (Valerius et al, 1991), in numerous lung infections e.g. pentamidine for the treatment of pneumocystis carinii, a condition common in patients with AIDS, (Montgomery et al, 1987) in vaccination against influenza and tuberculosis, for the delivery of local anaesthetics, surfactants and prostaglandins.

When drugs are delivered for local action in the lung by means of an aerosol, doses much less than those necessary for the same action delivered via gastrointestinal or parenteral routes can be employed. This has the advantage that the systemic adverse effect profile is reduced and the in cases where oral bioavailability is poor, e.g. SCG, (Boyes, 1989) or where the drug is metabolised rapidly when administered orally e.g. isoprenaline, it provides an alternate means for delivery.

Interest is growing in the lung as a route for drug delivery, for conditions other than those associated with the lung. The physiology of the lung is such that there is a potential for rapid drug absorption and hence a faster onset of action, since the small airways of the lung have a large surface area, (Gonda, 1988). This has been exploited in the treatment of migraine with ergotamine. Other advantages of drug delivery via the lung lie in the fact that the first pass metabolism by the liver can be circumvented. Although the lung is an organ of metabolism and contains its own proteases, the activity is intracellular and the competitive absorption kinetics are rapid. It has
therefore, been used as a route for peptide delivery and may be used as an alternative route to injectables (Mellem et al, 1991).

1.2 Anatomy and Physiology of the Respiratory Tract

The main purpose of the respiratory tract is to provide ventilation to the body. It acts as a gaseous exchange mediator between the body tissues and the atmospheric surroundings. Oxygen is inspired and passes into the blood stream whilst carbon dioxide passes back out in the expired air.

The respiratory tract can be divided into upper and lower regions or into conducting and respiratory regions. The upper respiratory tract comprises of the nose, throat, pharynx and larynx, whilst the lower consists of the trachea, bronchial tree and the alveolar regions (fig. 1.1). The whole organ not only allows gaseous exchange but also is designed to efficiently remove any foreign particles inadvertently inhaled.

Air is inhaled through the nostrils or nares, the entrance of which are lined with skin containing sebaceous glands and strong filtering hairs. The remainder of the nasal passage is ciliated, highly vascular containing many mucus glands and goblet cells, with underlying clumps of lymphoid tissue. Nasal secretions are swept backwards by mucociliary action towards the throat and swallowed.

The nasal passages lead into the pharynx, which communicates with the buccal cavity, and subsequently into the larynx which joins the trachea. It is in the nasopharyngeal regions that the inhaled air is warmed to between 30-33°C and humidified, the local relative humidity being around 100%. The larynx acts as a flow regulator. The reduced cross sectional area of the larynx compared to the nasal and pharyngeal passages causes airway resistance and as a consequence turbulence, secondary eddies and inertial impaction (see below). As the airstream enters the larynx from the nasopharynx it is required to change direction by about 90° another cause of inertial impaction of particles in this region.
The trachea, the first part of the lower lung division, is D-shaped in cross section, supported by 16-20 cartilaginous rings and has a diameter of around 15-20 mm, which increases during inspiration and decreases with expiration. The trachea branches into two bronchi, to the right and left lungs respectively. The right bronchi is much wider than the left and leaves the trachea at a smaller angle (35°) compared to the left (73°) (Clarke, 1984) and therefore is much more likely to receive inhaled material. The two main bronchi branch further into three lobar bronchi on the right and two on the left, which in turn subsequently divide further into smaller bronchioles (0.5-0.8 mm diameter) and even smaller terminal bronchioles (0.3-1.0 mm diameter). At this point
the limit of the conducting airways is said to be reached and the function of air conduction is replaced by gaseous exchange. The terminal bronchioles divide into respiratory bronchioles, of which there are over one hundred thousand in the human lung. These finally connect with the alveolar ducts leading to the alveolar sacs. The alveolar sacs are said to contain between $2-6 \times 10^8$ alveoli which produces an estimated surface area of between 70-80 m$^2$ in the human male adult (Bowman and Rand, 1980). The bronchioles differ from the main bronchi in that they do not contain cartilaginous rings.

The epithelium of the trachea and the main bronchi consists of tall columnar ciliated cells, mucus secreting goblet cells, non-ciliated cells with a brush border and short basal cells. Any fine, insoluble particles that are trapped by mucus in this region are swept upwards from the lungs by the beating cilia and swallowed. The epithelium of small bronchi and bronchioles consists largely of ciliated columnar cells with only a few goblet cells, known as Clara cells, which secrete a protein rich exudate. In the epithelium of the respiratory bronchioles and alveolar ducts the ciliated cells are more squat in shape and the number of Clara cells is increased. The alveoli contain phagocytic cells and the mechanism for insoluble particle removal from this region is phagocytosis. In addition to the phagocytic cells, pneumocytes are present. Type II pneumocytes which occupy approximately 3% of the alveolar surface synthesize and secrete lung surfactant, which is responsible for the regulation of the surface tension at the alveolar surface and hence prevent lung collapse.

1.3 Drug Deposition in The Lung
Aerosol delivery has the disadvantage that only a small proportion of drug available in current formulations is deposited in the lung. Deposition is in the order of 10% or less (Newman et al, 1984) and dosaging is often irreproducible (Gonda and Byron, 1978). The main feature concerned with drug delivery to the lung is one of particle deposition (quantity and position) within the lung. Much work has been done to establish the mechanism of deposition and the absorption from lung sites. Many
models have been developed for in vitro aerosol evaluation and predicting in vivo behaviour (section 4.1.1).

For a drug to be absorbed, for either local or systemic action, it must be deposited deep in the lower respiratory tract (Kirk, 1986). The total surface area of the adult lung is 30-100 m², (Gonda, 1988). Most of this surface (70-80 m²) is in the aveolar regions of the lung, which also have a high concentration of capillaries for rapid gaseous exchange. Therefore any drug deposited in this region has the opportunity for rapid absorption, (Gonda, 1988). Drug deposition in the lung is dependent on three factors; the physico-chemical properties of the drug, the patient (breathing patterns and physiology) and the liberating device (formulation and design). The most important physical property of the drug is usually its size. Aerosols are often classified in terms of their mass median aerodynamic diameter (MMAD) and the geometric standard deviation (GSD or \( \sigma_g \)) of their median aerodynamic diameter. The MMAD, is the diameter of a sphere of unit density \( (1 \text{ kg dm}^{-3}) \) which has the same terminal settling velocity as the particle in question. It takes into account the diameter and the density of the particles, being the product of the mass median diameter and the square root of its density (Gonda, 1988, Newman and Clarke, 1983).

The particle size is considered to be the most important determinant for the prediction of the site of deposition within the lung (Pritchard, 1987). Fundamental mechanisms of particle deposition which relate to size have been developed and are described below. There are three main mechanisms responsible for particulate deposition in the lung; impaction, gravitational sedimentation and diffusion.

(i) **Inertial Impaction**

Inertial impaction is dependent on a particle’s mass and velocity, that is, its momentum. Particles are carried by the airstream entering the lung. When an obstacle or a bifurcation in the lung passage is encountered, the airstream is caused to change direction. The inertial force of the particle resists this change causing the particle to proceed, for some distance, in its original path. A particle having a high
momentum will therefore deposit on the lung surface rather than follow the changing air stream. This mechanism for deposition is especially important for large particles, having a diameter of 10 \( \mu \text{m} \) and greater and is common in the upper airways. It is the principle mechanism for deposition in the nose, mouth, pharynx and larynx and the large conducting airways down to 2 mm in diameter (Newman and Clarke, 1983). As the air stream proceeds into the lung it encounters more and more branching of the conducting airways, the successive bifurcations cause the velocity of the air to decrease and impaction becomes a less important mechanism for deposition.

(ii) Gravitational Sedimentation
Gravitational sedimentation is dependent on the mass and residence time of a particle. Particles settle in the airways under the influence of gravity, during breath holding or tidal breathing. The settling velocity of a particle increases with the square of the aerodynamic diameter. Sedimentation is an important mechanism for deposition in the small airways, less than 2 mm in diameter and the alveoli (Newman and Clarke, 1983), for particles that have escaped deposition by impaction, in the size range 0.5 \( \mu \text{m} \) and 3 \( \mu \text{m} \). Particles with diameters below 0.5 \( \mu \text{m} \) have too small a settling velocity to be captured by this mechanism, unless they are held over a prolonged period of time.

(iii) Diffusion
Collision and bombardment of other molecules in the respiratory tract cause Brownian motion. Resultant movement of particles is from high to low concentrations and as a consequence particles move from the aerosol cloud to lung walls. The rate of diffusion is inversely proportional to the particle size, therefore it is the predominant mechanism for particles smaller than 0.5 \( \mu \text{m} \). It should be noted that many of the particles having a diameter less than 0.5 \( \mu \text{m} \) may be exhaled due to the fact that they are too small to be deposited by gravitational deposition and impaction and are too large to diffuse through the stagnant air to the pulmonary surface and are therefore, carried out during normal breathing (Gonda and Byron, 1978).
Figures 1.2 and 1.3 show the relationship between anatomical site and particle size for lung deposition. The optimal MMAD for lower lung deposition has been reported to be around 3 μm (Gonda, 1988), 1-5 μm (Hilman, 1991), 0.8-3 μm (Aerosol Consensus Statement, 1991).

Other physico-chemical properties of drug particles such as shape, density, electrostatic charge, crystallinity and hygroscopicity affect their deposition profile. Extreme shapes such as fibres may physically catch onto the walls as they pass through the respiratory tract. The density of a particle will affect its MMAD, mentioned above and hence its deposition. An electrostatic charge on a particle will induce an opposing charge within the walls of the respiratory tract and thus cause the particle to be attracted to the walls by coulombic forces (Pritchard, 1987). The crystallinity of a drug may affect its solubility and in the case of dry powder inhalers, mention later, its ability to be liberated from a carrier material. Hygroscopic particles have been noted to increase in diameter on entry into the humid airways of the respiratory tract. As a consequence particles that on first inspection have the correct MMAD for lower lung deposition may not in fact deposit there (Hiller et al, 1980, Hicks and Megaw, 1985). Hygroscopic growth is governed by the mass transfer to and the latent heat transfer from the particle surface. The process is dependent on the physico-chemical properties of the particle, the local water content (relative humidity), temperature and the air flow pattern in the surrounding airways.

As a particle enters the respiratory tract the change from an ambient to a high relative humidity (estimated at 96-99.9%, Pritchard, 1987) causes water condensation onto the particle, which continues until the vapour pressure of the water on the surface of the particle equals that of the surrounding atmosphere.
For insoluble materials hygroscopic growth is insignificant as only a thin, water film will be formed on the surface of each particle. In the case of water soluble materials however, hygroscopic growth will affect its deposition, causing particles to deposit higher in the respiratory tract. As a water soluble particle enters the respiratory tract a solution is formed on its surface. The vapour pressure of the solution is lower than that of pure solvent at the same temperature and thus the driving force created by the difference in the two values causes the particle to continually absorb water until equilibrium is reached. The final diameter reached is constrained by the Kelvin effect and is a function of the particle’s original diameter (Pritchard, 1987).
Patient dependent factors such as breathing patterns; inhaled volume, flow rate and breath holding, and lung physiology effect particle deposition. The greater the inhaled volume the more peripherally the particles will be distributed in the lung (Newman and Clarke, 1983). An increase in flow rate however causes more particles to be deposited higher in the pulmonary tract, by inertial impaction. Manipulation of the breathing pattern for example, breath holding after actuation of the aerosol device, has been shown to increase deposition of particles of aerodynamic diameter 0.5 \( \mu \text{m} \) and less, as a consequence of the prolonged residual time of the particle, allowing sedimentation to take place, (Aerosol Consensus Statement, 1991). These particles without breath holding would normally be exhaled. The ideal method for inhalation is one of a slow (0.5 \( \text{L sec}^{-1} \)) deep inspiration to total lung capacity, followed by breath holding (Aerosol Consensus Statement, 1991). Inter-subject variation in regional distribution of aerosols has been noted and thought to be a consequence of anatomical and physiological differences (Vidgren et al, 1987c). Narrower airways
such as those found in children and obstructed adult airways, lower the distal aerosol deposition (Aerosol Consensus Statement, 1991). Changes, caused by disease states may also affect the deposition profile (Byron, 1987).

The formulation of the drug and the aerosol device design from which it is liberated also have an influence on deposition and are discussed fully below.

1.4 Aerosol Formulation

There are currently three main types of aerosol formulation devices these being, metered dose inhalers (pressurised, propellant powered), dry powder inhalers (both of which are described in more detail below) and nebulisers (air jet and ultrasonic, electrically powered).

1.4.1 Metered Dose Inhalers

Metered dose inhalers (MDI), first introduced in the mid 1950s are the most frequently used inhalers. In these devices the drug substance is either dissolved, with or without the aid of a cosolvent (Kirk, 1986) in a liquid propellant mixture or more commonly, micronised drug is suspended in a liquid propellant mixture together with other excipients, including surfactants. The formulation is presented in a pressurised (typically 300 to 500 kPa, Newman, 1991; Matthys, 1990), metering dose canister, (fig. 1.4). A predetermined dose is released as a spray on actuation of the metering value. When released from the canister the formulation undergoes volume expansion in the passage and forms a mixture of gas and liquid before discharge from the orifice. A high speed gas flow then helps to break up the liquid feed into a fine spray of droplets (Kim et al, 1985). Currently, propellants consist of various chlorofluorocarbons (CFC) (identified by a numbering system), all of which have different physical properties and contribute to the vapour pressure within the canister by differing degrees. Formulations generally consist of blends of chlorofluorocarbons 11, 12, and 114 (usually in the ratio of 1:2:1, giving a vapour pressure of 374 kPa at 20°C, Newman et al, 1984) together with a surfactant such as a sorbitan ester, oleic
acid or lecithin, which is present for the uniform suspension of the drug and lubrication of the value device (Byron, 1986). The surfactants also aid the stability of suspension formulations by preventing agglomeration of the drug and its adherence to the walls of the canister (Kirk, 1986).

An ideal MDI is one containing a stable, homogeneous suspension, which is metered accurately and reproducibly (Byron, 1986). The advantages of MDIs lie in their portability, simplicity, efficiency of dispersion, cheapness and disposability. Many doses are stored in a small canister. Dose delivery is reproducible, the vapour pressure, within the canister, remaining constant until empty. Chemical stability of oxygen labile drugs in a MDI is good as a consequence of the inert conditions created by the propellant vapour. The presence of moisture however, may effect the chemical stability of the suspension and the solution formulations (Kirk, 1986), this can be overcome by addition of the desiccant, anhydrous sodium sulphate to the formulation. The water content can be reduced to a minimum by suitable manipulation of the formulation. Other stability problems such as surface drug caking and increase in drug particle size with time, can all be overcome by added excipient or manipulation of the formulation procedure (Kirk, 1986). The MDI device is hermetically sealed and therefore, has the added advantage of guarding against microbiological contamination.

MDIs however have many disadvantages: MDIs are inherently inefficient in their drug delivery, less than 10% of the drug being deposited in the lower lung (Vidgren et al, 1988b). Analysis of nine MDIs carried out by Bouchikhi et al (1988), showed tracheobronchial deposition to lie between 3 and 11.5%. On actuation the first propellant droplets exit at a high velocity, the velocity may exceed 30 m sec\(^{-1}\) (Newman and Clarke, 1983; Newman, 1991). Much of the drug is lost as a consequence of impaction in the oropharyngeal areas (Paronen et al, 1987). The mean droplet diameter emitted from the device is typically in excess of 40 µm (Moren and Andersson, 1980), propellants do not evaporate at a rate sufficient for the droplet diameter to decrease to a size (one nearer that of the original micronised drug) suitable for deep lung deposition.
It has been reported that the mean droplet size, 10-25 cm from the mouthpiece of the device, was 14 μm (Moren and Andersson, 1980), which explains the early sedimentation of larger droplets. Evaporation, such that the MMAD of the particles are closer to those of the original micronised drug, has been noted to occur some 5 seconds after actuation (Hiller et al, 1978). Vaporisation of the droplets is hampered by the low volatility component, propellant 11. Propellant 11 is a liquid at room temperature having a boiling point of 23°C and is present in concentrations of at least 25% in most formulations. This propellant is often included to allow formulation at room temperature, followed by "gassing" with the volatile components and is required, among other reasons, for valve operation. The supercooled droplets of propellant 11 in the humid environment of the respiratory tract may act as a nuclei for water vapour so further delaying the droplet size reduction. Although the practical significance of this on MMAD has been questioned (Kim et al, 1985).
Another disadvantage of MDIs, is one of the propellant action on the structure of the earth’s ozone and their contribution to global warming. Chlorofluorocarbon propellants pass through the earth’s troposphere layer into the stratosphere, where they are decomposed to yield chlorine atoms, which in turn catalyses the breakdown of ozone, (Kirk, 1986). A global ban on CFCs by the year 2000, set out in the Montreal protocol, will greatly affect MDI usage (Balmes, 1991). There has been much investigation into the search for alternatives to propellant 11, 12 and 114. Propellant 134a, a non ozone depleting, non flammable hydrofluorocarbon has been investigated as an alternative to propellant 12. This has similar physical properties to propellant 12 but is however, less chemically stable and presents other formulation problems such as being a poor solvent with regard to surfactants commonly used in MDI formulation (Dalby et al, 1990). Mixtures of propellant 11 and 134a have been shown however, to have potential. The currently approved alternative to propellant 11 is ethanol, this has low volatility and therefore may increase droplet size (Dalby et al, 1990). Other potential, non ozone depleting replacements tend to contribute to global warming. Alternative hydrocarbon propellants have the drawback of being highly inflammable (Dalby and Byron, 1992) and toxic on long term usage (Pierce et al, 1991). Compressed gases such as nitrogen dioxide, nitrogen and carbon dioxide are not able to maintain a constant pressure within the canister throughout its life time and as a consequence the reproducibility of the dose cannot be assured (Matthys, 1990).

The potential toxic effects of chlorofluorocarbons are also of some concern. CFCs have been shown to sensitise the myocardium to arthymogenic effects of adrenergic stimulation, in test animals. This study was performed in response to concern over the increase in death rates in asthmatic patients inhaling isoprenaline from an MDI. The plasma concentrations for this effect would require however, dosing many times above the recommended regime and therefore this is considered to be clinically insignificant effect (Pierce et al, 1991).
Correct operation of a MDI device by the patient is extremely important for drug deposition (Saunders, 1965). The actuation of the device should be co-ordinated with inspiration. Ideally the MDI should be actuated during the course of slow, deep inspiration (30 L min$^{-1}$), followed by a ten second period of breath holding, (Newman, 1991). Many patients find this difficult especially children and elderly adults (Matthys, 1990; Hilman, 1991). Also the initial shock of the cold propellant hitting the back of the throat on actuation, sometimes causes the patient to stop inspiration as a reflex action, so impairing the inhalation. Even using the correct inhalation technique it is only possible the deliver between 15-20% of the dose to the lungs (Newman, 1991).

Some of the disadvantages namely, breath-actuation co-ordination and the premature deposition of large propellant droplets can be overcome by the use of extension devices or spacers to the inhaler. Small aerosol reservoirs can be placed between the MDI actuator and the patient. The aerosol is discharged directly into the reservoir prior to inhalation. This allows the diluted (in air) particles to remain suspended for several seconds giving adequate time for evaporation of propellants, reduces the initial droplet velocity and removes the need for patient actuation-inhalation co-ordination. This is especially advantageous for drugs such as corticosteroids where high throat deposition leads to a higher incidence of local adverse effects, namely oral candidiasis. The disadvantage of extension devices is that they are bulky. The increase in deep lung deposition with a spacer device is dependent on the geometry of the spacer, the outlet valve, residence time of the aerosol within the spacer and the inspiratory flow rate of the patient (Matthys, 1990). The development of Autohaler® (3M Riker), which has an inspiratory demand valve that is, the device is breath actuated, has helped to overcome the co-ordination problems of the MDI (Newman et al, 1991), without the problem of adding bulk to the device. These inhalers however require a substantial inspiratory flow rate for operation. Another new device however, the Gentle-Haler® (Schering) has been developed to address the problem of the initial high velocity. The spray emerges from this device at a much reduced velocity and has been shown to reduce oropharyngeal deposition (Newman, 1991).
1.4.2 Dry Powder Inhalers

In dry powder inhaler (DPI) devices the drug powder is inhaled directly. The only other excipient may be an inert coarse carrier material, such as lactose. Currently there are two types of dry powder device, the single dose device, the most common being the Spinhaler® (Fisons) and the Rotahaler® (Glaxo) where the drug is delivered from a hard gelatin capsule placed in the device, and secondly the multidose device, such as the Diskhaler® (Glaxo) and the Turbohaler® (Astra).

Dry powder inhalers have several advantages over the MDIs. DPs do not contain any excipient, other than lactose, thus the question of CFCs is not a problem, (Aerosol Consensus Statement, 1991). DPs being breath actuated remove the problems of breath actuation co-ordination, reducing the incidence of inhaler misuse. In a study by King et al (1991) the percentage misuse of MDIs due to poor actuation-inhalation co-ordination was determined for a group of patients. The cost of the misused aerosol was also calculated. It was found that the percentage misuse fell from 68.4% to 17.5% with proper advice. All patients studied however, were able to use a DPI correctly. DPs have been shown to be especially advantageous for children (Cuss, 1988; Aerosol Consensus Statement, 1991). Although a high velocity of inspired air is required for DPI actuation, less drug deposits, by inertial impaction, in the throat regions. Particles follow the inspired air flow into the lower respiratory tract (Vidgren et al, 1988a). The clinical response of terbutaline (Osterman et al, 1991) and the in vitro deposition of salbutamol (Vidgren et al, 1992) from DPs has been shown to be as effective as that from MDIs. DPs also have the advantage that relatively large doses may be delivered. MDI formulations are limited by the volume of the metering value and the maximum concentration that can be suspended without causing clogging of the metering valves.

As previously discussed, for a particle to be deposited in the lower respiratory tract the MMAD must be between 10 and 3 μm or less (Gonda, 1988). Drug powders are often micronised by means of an air jet mill to a suitable respirable size.
Unfortunately the high energy powders produced have poor flow properties due to their static, cohesive and adhesive nature, (Kirk, 1986). The flowability of a powder is affected by its physical properties of size, size and shape distribution, particle shape, density, surface roughness, hardness, moisture content and bulk density. The most important factor for deposition is size. It has been demonstrated in earlier work, using the Spinhaler® DPI, that micronised SCG alone will not liberate from a gelatin capsule. Only when mixed with larger size fractions of between 30-60 μm, was the flow improved such that powder liberation from the capsule and the device was successful, (Bell et al, 1971). For this reason where the dose is presented in a hard gelatin capsule for use in unit dose DPIs, the micronised drug is mixed with a larger (30-60 μm) inert material usually lactose. This not only improves liberation of the drug from the device but also improves uniformity of capsule filling (Kirk, 1986).

Once liberated from the device the turbulent air flow, generated within the device should be sufficient for the deaggregation of the drug-carrier particles. Thus causing the larger carrier particles deposit, by inertial impaction, in the throat regions and the smaller drug particles to be carried with the inspired airflow into the peripheral respiratory tract. It has been noted however, that only part of the drug is released. Release was found to be improved by an increase in flowability as a result of a decrease in mean particle size of the carrier (De Boer et al, 1989). The cohesive and attractive forces between the drug and carrier depend on the chemical and physical properties of the materials and it is these that influence deaggregation (Vidgren et al, 1988d). Deposition is strongly dependent on the inhalation technique, formulation factors and design and construction of the device (Vidgren et al, 1988a; Vidgren et al, 1988b). The greater the turbulent air flow the more easily the powder is dispersed. Vidgren et al, (1988a) deduced that in the design of the device the smaller the diameter of the air channels within the device the greater the turbulent air flow.

The first DPI device to be developed was the Spinhaler® (Fisons) introduced by Bell and colleagues in 1971 (Bell et al, 1971), for the delivery of the prophylactic antiasthmatic drug, sodium cromoglycate (Intal®), (fig. 1.5). Each dose, contained in a hard gelatin capsule, is loaded individually into the device. The capsule is pierced
by two metal pins either side of the capsule. Actuation of the device is simple: inspired air flow through the device causes a turbovibratory air pattern to be created as a consequence of its activation of the loose fitting rotor. The rotor is mobilized at air velocities of 35-40 L min\(^{-1}\). The air stream produced causes the powder to be dispersed to the capsule walls and out through the perforations into the air, irrespective of orientation (Bell et al, 1971). The local irritation and lactose intolerance noted by some patients, by carrier deposition in the throat regions has lead to the development of DPI containing drug alone. An example of this is the pelletized formulation of SCG (Intal®) used in the Spinhaler® without dispersant. Edwards and Chambers (1989), showed the pelletized formulation to be as clinically effective as the mixed form and that emptying from the gelatin capsule was improved. The Spinhaler® device has been noted to be sensitive to formulation factors such as carrier size, with regard to its drug delivery (Vidgren et al, 1988a).

Another unit dose DPI is the Rotahaler® (Glaxo). The original design of the Rotahaler® (Glaxo) was described by Hallworth (1977), this however, was later redesigned, (fig. 1.6) to improve ease of use (Pover et al, 1982; Pover and Dash, 1985). The clinical effectiveness of the Rotahaler® has been described by Huntley et al, 1977. The Rotahaler® is a simple two piece device, developed for the delivery of salbutamol sulphate (Ventolin®) and beclomethasone diprornionate (Becotide®). Operation is again simple, the gelatin capsule is inserted into an orifice at the rear of the device. The two sections are rotated over each other causing a fin on the inner barrel to pull the two sections of the capsule apart, thus emptying the contents. The capsule contents are then simply inhaled through the mouth piece. The Rotahaler® has the advantage of operating at very low inspiratory flow rates (30 L min\(^{-1}\)) as a consequence of the low resistance to air flow within the device. The resistance to air flow is lower than that of the Spinhaler® and therefore requires a lower inspiratory velocity (Pover et al, 1982). The main disadvantage of the Rotahaler®, that is the individual loading of each dose, was overcome with the development of the Diskhaler® (Glaxo) (Pharmaceutical Journal, Jan. 1988 and Developments in Inhalation Therapy, 1988).
The drug (salbutamol sulphate or beclomethasone dipropionate) is mixed with a coarse lactose, but instead of capsules the mixture is presented as a circular foil blister pack. Each blister containing a dose, pierced before actuation.

Development of the Turbohaler® (Astra), fig 1.6, which was introduced to the UK market in 1988 (Pharmaceutical Journal, March 1988), overcame both the need for a carrier and the individual dose loading. The small device contains 200 doses of undiluted, micronised terbutaline, equivalent to the of a conventional MDI (Matthys, 1990). The drug flows from the drug reservoir down onto a rotating disc. The fine holes in the disc are filled and the excess drug removed by scrappers.
As the rotating disc is turned one metered dose is made available in the inhalation channel. The dose is then simply inhaled by the patient. The turbulent air flow created, breaks up any drug aggregates present. Both administration and clinical effect (a reflection of the deposition) of terbutaline sulphate delivered from the Turbohaler® were shown to be similar to that from a MDI (Newman et al., 1989). Response is increased with increase in inspired air flow rate, causing an increase (due to deaggregation) of smaller particles, less than 5 μm (Persson and Wiren, 1989). The Turbohaler® however, has been shown to require a higher inspiratory effort (work done) than the Diskhaler®. This is believed to be a function of the internal resistances of each device, (Sumby et al., 1992).
The stability of dry powder aerosols has been questioned. In MDIs, drugs are suspended in propellants which provide an inert atmosphere. Drug powders in DPIs are exposed to atmospheric conditions. Humidity for example, may cause clumping of the powders on storage (Aerosol Consensus Statement, 1991). On actuation hygroscopic growth within the humid lung airways, may cause changes in particle size and density. Measured particle size was seen to alter 1.4 fold compared to 3.6 and 4.1 fold for droplet aerosols, when measured at two different humidities, 16-21% and 95-98% (Hiller et al, 1980). This suggests that MDIs may be more unstable than DPI on release. Vibration during storage, such as transportation, may increase drug cohesion and drug-carrier adhesion (Kirk, 1986). Carriers should be formulated so that drug agglomeration is minimised.

Drug delivery from dry powder inhalers have several disadvantages; usually twice the dose is required for delivery than that from a MDI, (Byron, 1986; Byron, 1987).
Pharmacokinetic studies using the Spinhaler® showed only 5% of the dose to reach the lung (Walker et al, 1972). Micronised powders adhere strongly to surfaces they come into contact with and themselves. Because aggregation is so strong dose metering is not always reproducible (Byron, 1986; Moren, 1987) Liberation from the device and deaggregation of the particles are limited by the patients ability to inhale, which, in the case of lung disorders, may be affected, (Moren, 1987). An increase in turbulent air flow created by an increase in inhaled air velocity increases the deaggregation of the emerging particles, but also increases the potential for inertial impaction in the throat regions, thus a compromise has to be obtained. Only a limited number of drugs may be delivered using DPIs because of stability problems (Aerosol consensus Statement, 1991).

1.5 Controlled Particle Size Preparation

Controlled particle size preparation can be divided into two main techniques, size reduction from a larger, coarser material for example, milling and grinding and secondly production of particles from a solution for example, controlled precipitation and crystallisation.

Powders for formulation into dry powder inhalers are usually prepared by micronisation, a milling process. The typical mill used is the fluid-energy mill (air-jet mill) (Morén, 1987; Vidgren, 1988c), (fig. 1.8), this produces fine particles within a relatively narrow size distribution. These mills have no moving parts but rely on the particles breaking up as they collide with each other when subjected to high velocity (high energy) elastic fluid streams (usually air, steam or inert gas). The relatively coarse powder material is fed into the mill via a venturi feeder. The powders are introduced directly into the jet stream of elastic grinding fluid, which is introduced under pressure (25-300 lb in²), through nozzles at the base of the mill. The rapidly circulating gas flow causes the powders to be transported upwards through the tract.
Chapter One - Introduction

Figure 1.8 Fluid Energy Mill.

The extreme turbulent flow causes the particles to rapidly accelerate to high velocities so that on collision the impaction is so great shattering of the particles occurs. The particles are carried towards the top of the mill where they are separated, the smaller particles are carried out with the gas flow to a collection chamber or a bag, whilst the larger particles continue to move around the mill as a result of their momentum and the centrifugal force created. These mills have the advantages of the temperature remaining low due to the cooling effect of the elastic fluid as it expands in the grinding chamber and no contamination to the product as a consequence of the mill not having moving parts. The disadvantages are that the feed rate has to be carefully controlled to avoid clogging of the device and that the mills are usually only large enough to handle small quantities of material at one time.
Chapter One - Introduction

Materials to be milled to a micron size usually require to be pre-milling. Larger particles may require particle size reduction in stages to produce the final product, because the micronizing mill will not accept very large particles (Ripple, 1985). Therefore, although the fluid jet mill may produce a product free from contamination, it may be present from previous processing. Particle size reduction has the added disadvantage that particles can only be comminuted to a critical size, below which particles are plastically deformed and further energy input is wasted (Kendall, 1978).

Controlled particle size production from solution by controlled precipitation and crystallisation can be carefully regulated to produce specific particle properties. Similarly spray drying could be manipulated to control particle size and physico-chemical properties. Spray drying has been used by the pharmaceutical industry for many years as means of producing powders with predetermined properties, especially in the case of thermolabile materials. Manipulation of the process has been used to alter the physico-chemical properties of both drugs and excipients and as a consequence improve aspects of their formulation. Examples of this are tableting (especially granulation), microencapsulation and complex formation (Broadhead et al, 1992). More recently, spray drying has been used indirectly for DPI formulation in a co-precipitation technique, to radiolabel salbutamol sulphate (Vidgren et al, 1992) and SCG (Vidgren et al, 1987a) for dispersion studies with regard to inhaler design comparison, (Vidgren et al, 1988a; Vidgren et al, 1990) and comparison between MDI and DPI devices (Vidgren et al, 1988b; Paronen et al, 1987). The properties of spray dried SCG were shown to be superior to that of the micronised powder for inhalation purposes (Vidgren et al, 1987b; Vidgren et al, 1988c). Spray drying was seen to improve particulate powder properties such as particle size, crystallinity and solubility, without causing chemical decomposition (investigated using mass spectrometry). The particle size was noted to be not only smaller but also of a narrower distribution than that obtained from micronisation (Vidgren et al, 1987c). It has been noted that a monodispered aerosol in the correct size range will give a better deposition profile than a heterodispersed one. On spray drying the crystallinity of the drug was seen to alter and an amorphous powder was produced (confirmed using X-ray diffraction
techniques) (Vidgren et al, 1989). This is advantageous in dry powder aerosol formulation since a decrease in crystallinity is also accompanied by a decrease organised, tight binding between the carrier particles and the drug. This was thought to be the reason for the improved in vitro deposition of the spray dried material. The solubility of SCG was noted to increase, this has the advantage of increasing dissolution of the drug but the disadvantage of increasing the potential for moisture uptake during storage and consequently affecting stability and inhalation properties. At high humidities spray dried particles of SCG were seen to recrystallise to form larger aggregates (Vidgren et al, 1989).

Spray drying of other pharmaceuticals for example phenobarbitone and hydroflumethiazide has shown to produce small, spherical particles with narrow size distributions (Corrigan et al, 1983). In the light of the previous work mentioned, the manipulation of the physio-chemical properties that can be performed using the spray drying process make it an appropriate possible alternative to micronisation for controlled particle size reduction, for drug used in dry powder inhalation. The spray drying process is discussed more fully in Chapter 2.

1.6 Research Aims
The aims of this research were to investigate the formulation aspects of dry powder aerosol inhalers. To investigate spray drying using a Büchi 190 mini spray dryer as a method for the production of small drug particles in the respirable size range (≤ 10 mm). To rationalise the spray drying process with respect to the production of powders suitable for dry powder inhalation formulation. To measure and compare the physico-chemical properties of the spray dried and micronise powders. To measure surface energies of powders and relate the values to physical powder properties and in vitro deposition and liberation from carrier materials.
Chapter Two

Spray Drying
2.1 Introduction

Spray drying is a process by which a solution, suspension or paste is transformed into a dry particulate powder. Spray drying is not only a drying process but can also have a dramatic effect on the powder produced. That is, it is a means by which materials can be altered to different physico-chemical form as is the case with spray dried foodstuffs. The spray drying operation is manipulated to produce products for all the major industries, these are as diverse as clays and paints to foodstuffs and pharmaceuticals. In pharmaceuticals it has been used successfully to alter physico-chemical properties to improve formulation, for example improvement of compressibility of a powder for tablet manufacturing (Fell and Newton, 1971c).

Historically, spray drying dates back to 1865 when it was mentioned in connection with egg handling. But it was Samuel Percy in 1870's who is believed to be the first person to describe in detail the drying of products in a spray form in a patent entitled, "Improvements in drying and concentrating liquid substances by atomisation". Industrial applications of importance occurred in the 1920s in the milk and detergent industries for which spraying is still famous (Masters, 1990). An important feature of spray drying is the rapid drying making it particularly useful for thermolabile materials.

2.1.1 Spray drying Operation.

The spray drying process can be divided into four stages these are as follows:

i) Atomisation of the feed.

ii) Spray-gas contact (mixing and flow).

iii) Drying of the spray.

iv) Separation of the dried product from the air.
2.1.1.1 Atomisation

Atomisation is the central process around which spray drying is based. It is essentially the transformation of a liquid feed into a fine spray, hence the term atomisation. Atomisation serves two purposes; the first being to provide a feed which has a high surface area to mass ratio, creating the ideal evaporating conditions and secondly to produce a product with certain physical characteristics such as shape, density and particle size distribution (Marshall and Seltzer, 1950a). The ideal spray for drying is one with small droplets of equal size.

The mechanism of atomisation of a feed depends primarily on the design and source of energy of the atomising nozzle through which the feed passes. All atomisers require an energy source to break up the bulk feed, this energy can be provided in the form of centrifugal, pressure, kinetic and less commonly, sonic or vibratory energy. The minimum energy for atomisation is that required to create a new surface (eqn 2.1) (Marshall and Seltzer, 1950a).

\[ P = A \sigma \]  
\textit{Equation 2.1}

Where \( A \) = net average area created per min, \( \sigma \) = surface tension \( \text{kg m}^{-1} \), \( P \) = power required to create a new surface, \( \text{m kg min}^{-1} \).

This however, only accounts for a small fraction of the total energy used by the atomizer during the spray drying process. The most commonly used nozzle design types are as follows:-

a) Rotary nozzles: These can be classified into two types; atomising wheels and discs. Both types utilize centrifugal energy for atomisation.

b) Pressure nozzles: With this type, the feed is fed into the nozzle, via a swivel chamber, under pressure. The energy source is kinetic, converted from the pressure energy supplied. The feed being issued from the nozzle orifice as a high speed unstable film which readily disintegrates to form a spray.

c) Pneumatic (two fluid) nozzles: These rely on kinetic energy. The feed is passed into the nozzle together with a gas, usually air. High velocities are generated within
the nozzles causing the feed to break up into a fine spray. There are two ways in which the feed can be mixed; internally where the feed and the gas are mixed within the nozzle or externally where the gas is mixed within the feed as it emerges from the nozzle. The selection of atomiser depends on the type of feed and product characteristics required. The atomiser nozzle used for this research was a two fluid (pneumatic) nozzle, with internal air-feed mixing. Pneumatic nozzles have the advantage of producing homogeneous sprays of a small droplet size (Gretzinger and Marshall, 1961) over a range of operating conditions and feed types. The mechanism of atomisation involves the impaction of a high velocity gas on the bulk feed. The gas creates high frictional forces over the liquid surfaces causing feed disintegration into spray droplets. Although the overall break up process of the feed involves complex situations of liquid instability, due to the presence of the gas, it can be simplified into a two stage process. The first stage being, tearing of the liquid into filaments and large droplets and the second, the breaking of these into smaller droplets, so completing the atomisation (Castleman, 1931). The whole process is influenced by the physical properties of the feed solution, such as, surface tension, density, viscosity and gaseous flow properties of velocity and density (Masters, 1990). The nozzle design type used for this research was such that the optimum frictional velocities between the compressed air and the feed solution were achieved by directing the air flow onto unstable film sheets caused formed by rotating the liquid within the nozzle (fig. 2.1). This type of internal mixing has the advantage, over external mixing, of a high mass energy transfer.

It should be noted that non-uniformity in atomiser performance can be caused by non uniform feed concentration, clogging of the nozzle or crust formation, leading to fluctuations in the outlet temperature and bulk density (Marshall and Seltzer, 1950b)
2.1.1.2 Spray-gas contact

The stage following atomisation is the mixing of the atomised feed with the drying gas, in this case air. The manner in which mixing occurs bears a strong relation to the efficiency of the spray drier as noted by Marshall and Seltzer (1950b). They suggested that, because evaporation times are very short, the spray-air mixing time should also be short if the benefits of atomisation are not to be lost. The characteristics of air-spray mixing determine the evaporation time, the optimum residence time of the droplet in the chamber and the quantity of wall deposition of semi-dried product (Masters, 1990).

Spray-air mixing is largely dependant on the way in which the spray is emitted from the nozzle and the air flow pattern into which it is projected. Therefore, the design of the nozzle and the dryer chamber are an important factor. The way in which the drying gas enters the drying chamber can be classified into three design types; co-current, counter current and mixed flow. Co-current flow occurs when both the...
atomiser and the air flow disperser are positioned in the same area of the drying chamber. This is the case with the Büchi mini spray drier, used in this research, where the atomiser and the air disperser are positioned in the ceiling of the drying chamber. The air is passed through a sieve plate that surrounds the pneumatic atomiser. With counter current designs, the atomiser and the air disperser are situated at opposite ends of the drying chamber. Mixed flow chambers combine both co-current and counter current conditions during the drying procedure. This can be achieved in one of two ways, the spray flows in one direction whilst the gas flows in two, the inlet, outlet and atomiser all being positioned at the top of the chamber. The second method of achieving mixed flow conditions is to have the spray flowing in two directions whilst the air flows in one. In this case the atomiser is situated at the base, the feed is sprayed up into the gas and the product collected from the base.

Feed-air mixing is dependent on the flow of the atomised feed as it emerges from the nozzle and into the drying column. The flow of the droplets can be considered in three distinct stages; release from the atomising nozzle, deceleration and free falling, under the influence of the drying air. When first released from the nozzle, droplets are carried forward by the momentum of the spray and expanding atomising air. They travel at speeds far exceeding the surrounding drying gas. This is especially true of the spray emitted from a pneumatic nozzle, where the deceleration is much slower due to the dispersing atomising air that carries the droplets. The distance the droplets travel before obtaining the surrounding air velocity depends on, amongst other factors, their size, shape and density. Fine sprays are considered to be under the complete influence of the surrounding air. Once released from the nozzle frictional forces of the surrounding air and forces of gravity come into play, such that the droplet velocity decreases until it reaches that of the surrounding air. Several equations have been derived to predict the movement of a representative drop in the drying chamber, under certain conditions (Masters, 1990).
2.1.1.3 Drying

Drying is the removal of water or solvent from the feed to leave a nearly completely dry product. Drying of the atomised spray is by evaporation of the free moisture from the feed to the surrounding air. It is essentially the simultaneous mass and heat transfer between the spray and the surrounding gas, driven by the difference in water vapour pressure at the temperature at the surface of the droplet and the partial pressure of the water vapour of the surrounding air. Heat for evaporation is transferred by conduction and convection from the hot gaseous atmosphere to the droplet surface, while the vapour is transferred by diffusion and convection back to the surrounding gas (Marshall and Madison, 1955).

Moisture within a feed can exist in one of two forms, bound or unbound. Bound moisture is that which; is present in the small capillaries of the solid, adsorbed onto the surface of the solid, exists as solutions in cell or fibre walls or is chemically combined with the solid. The remaining moisture is the unbound moisture. In the case of non-hygroscopic materials however, all the moisture exists in the unbound form. Bound moisture exerts an equilibrium vapour pressure lower than that of pure water at the same temperature, whilst unbound moisture exerts a higher vapour pressure. Equilibrium moisture is the moisture of a feed when in equilibrium with the partial pressure of the vapour of its surroundings. The free moisture is the moisture that is excess to the equilibrium moisture and includes both bound and unbound moisture. It is only the free moisture of the feed that can be transferred by evaporation.

The rate of drying is thought to be dependent on a multitude of factors; temperature, humidity, velocity of the gas, the temperature, the number, size, size distribution of the droplets and the nature of the materials dissolved in the drops (Newton, 1966). The physical properties are greatly influenced by the drying rate, (Marshall and Madison, 1955).
Generally the evaporation process during spray drying can be split into several stages with differing rates, (fig. 2.2) The first stage, (a), occurs as soon as the droplet comes into contact with the drying medium. The droplet surface temperature increases until a state of equilibrium between the droplet surface and the air is achieved. The second stage (b), is one of constant evaporation, where moisture migrates from the interior, by means of diffusion aided by capillary action, to the exterior, to maintain saturation at the surface. The length of this stage depends on the temperature driving force and the internal mass transfer mechanism. The higher the drying air temperature and feed concentration, the shorter the constant drying rate will be (Crosby and Marshall, 1958). When the movement of moisture from the centre of the droplet is no longer sufficient to maintain saturation at the surface then the critical point (c), is said to have been reached. After this point the drying rate is decreases, accompanied by an increase in droplet temperature (fig. 2.3). When the droplet becomes completely dry, no longer containing any areas of local wetness, the evaporation rate decreases further, (d), the droplet surface providing resistance to drying. This rate is seen to decrease until the equilibrium moisture content is reached. The product however, is usually removed from the dryer before equilibrium is reached.

Figure 2.2  A Graphical Relationship between Drying Rate and Moisture Content
(Adapted from Masters, 1990).
Much work has been done to mathematically characterise the heat and mass transfers during evaporation. For example, the process of heat transfer from the surrounding air to a stationary spherical droplet was shown to be represented by the dimensionless number, \( \text{Nu} = 2.0 \), by Langmuir (Newton, 1966, Masters, 1990) where \( \text{Nu} \) is the Nusselt number (see eqn. 2.2).

\[
\text{NU} = \frac{h_c D}{k_d}
\]

Equation 2.2

Where \( h_c \) = convection heat transfer coefficient, \( D \) = droplet diameter and \( k_d \) = average thermal conductivity of surrounding air.

In the past, estimations and equations have used pure liquid droplets (water) as representative models under boundary layer theory conditions and it is these that form the basis of the understanding of the evaporation process. The boundary layer theory states that the evaporation rate for a droplet moving with zero velocity is identical to evaporation in still air conditions. From these equations it can be concluded that the rate of evaporation of a single droplet is proportional to the square of its original
Chapter Two - Spray Drying

diameter as it leaves the atomiser rather than its surface and the absolute evaporation rates from large droplets are greater than those from small droplets. In the case of droplets moving relative to the surrounding air the resulting flow conditions influence the evaporation rate. Evaporation rates increase with increase in relative velocity between the droplet and the surrounding air due to evaporation caused by convection in the boundary layer of droplet. The equations proposed by Ranz and Marshall published in 1952 (eqns. 2.3 and 2.4) are thought to be the most reliable and are the most commonly used, (Manning and Gauvin, 1960; Newton, 1966; Masters, 1990).

\[ N_u = 2.0 + 0.60 \left( \frac{N_{Re}}{} \right)^{\frac{1}{12}} \left( \frac{N_{Pr}}{} \right)^{\frac{1}{3}} \]  

\textit{Equation 2.3}

\[ N_{U'} = 2.0 + 0.60 \left( \frac{N_{Re}}{} \right)^{\frac{1}{12}} \left( \frac{N_{Sc}}{} \right)^{\frac{1}{3}} \]  

\textit{Equation 2.4}

Where \( N_u \) = Nusselt number, \( N_{U'} \) = Modified Nusselt number, \( N_{Re} \) = Reynolds number, \( N_{Pr} \) = Prandlt number, \( N_{Sc} \) = Schmidt number (see Appendix 2 for definitions).

These equations are not however without their limitations. For example the internal circulation of the droplets caused by the swirling air conditions causes a reduction in the boundary layer and so increases the evaporation rate. When considering the evaporation from a droplet under relative velocity conditions the deceleration period after release from the atomiser must also be considered. A droplet will undergo considerable evaporation in the time that is taken for it to decelerate to a state where it is completely under the influence of the surrounding air. Equations developed by Frossling (Masters, 1990) characterise this phase of evaporation. However the diameter of a pure liquid droplet in motion changes, causing changes in the deceleration rate to occur. Evaporation produced during these changes can only be
calculated using a stepwise method, unless the humidity gradient drop is small in which case the changes in the diameter can be considered to be negligible.

The drying features of a droplet containing dissolved solids differs completely from that of a pure liquid due to the solid material formation at the droplet surface. Dissolved solids reduce the vapour pressure of a solution and the vapour pressure driving forces are reduced, (Sjenitzer, 1952), as a consequence the evaporation rate is reduced. The pattern of drying is similar to that described above in that there is an initial constant rate of drying, where the droplet surface can be thought of as a saturated solution. The critical value when the drying rate ceases to be constant occurs when the presence of a solid phase forming on the surface is first seen. Movement of moisture from the interior to the surface is inhibited by the resistance caused by this solid forming phase. At this phase a simultaneous increase in droplet temperature occurs, as described earlier. The next stage of evaporation depends on the air temperature and the liquid inside the droplet. For example if the temperature of the air is above the boiling point of the liquid inside the droplet, the liquid vaporises. When the solid phase forms a crust around the droplet surface, pressures within the droplet increase. If the crust is porous then the vapour will escape, if not then rupturing, even disintegration may occur. The type of crust formed determines the drying mechanism, rate and shape of the final particle produced (Charlesworth and Marshall, 1960; Marshall and Madison, 1955).

Although the basic principles established from characterisation of single droplet evaporation can be applied to a droplet within a spray, in reality the evaporation characteristics are very different, making application difficult. Typical evaporation characteristics of a spray are as follows; the majority of the evaporation is completed within the first few seconds simultaneously causing a rapid reduction in the surrounding air temperature and that the mean droplet size of a pure liquid decreases with time as the smaller droplets evaporate.
Chapter Two - Spray Drying

Any analysis of spray evaporation depends on defining a spray in terms of a representative median diameter and size distribution, relative velocity between the droplet and its surrounding air, droplet trajectory and the number of droplets present at any one time per given volume of air. These factors are difficult to determine especially around the atomiser region thus making experimental evaluation of the evaporation difficult (Masters, 1990). An incremental method of calculating the evaporation process of a spray was proposed by Marshall and Madison (1955). This method involves the splitting of the size distribution into smaller size bands and considering each band individually as the evaporation process proceeds and the average diameter of the spray decreases. The change of the average droplet diameter, over short intervals, for each selected group is calculated. Using short time intervals in the calculation it can be assumed that the droplet evaporation proceeds at the same temperature driving force. Once evaporation for each size band is considered a new distribution is drawn up and the process repeated until the evaporation process is completed. Calculations for simplicity are based on log normal size distributions under zero relative velocity conditions.

The vapour pressure lowering effect of dissolved materials is proportional to the droplet size. Because of droplet size distribution, resistance to moisture transfer seen at the critical point does not occur simultaneously. Analysis of evaporation of a spray is therefore, complex, the best method is still the stepwise method of calculation.

2.1.1.4 Product Separation and Recovery

The final stage of the spray drying process is the separation of the dried product from the airstream. Separation in an industrial environment must be both economical and safe, ensuring that the exhaust gases are free of airborne particles. This is especially important for closed dryer systems where the warm air is recycled through the air heater. Product separation may be in one or two stages. In two stage collection the majority of the product is collected in the chamber base and the fines are collected by a secondary filter system. This is known as a two point discharge system. The
amount of primary product separation depends on the chamber design, atomisation of
the product and drying air flow. The product is separated by cyclonic air flow set up
in a conical chamber base or by the ability of the particles to fall out of the air flow
on to a flat chamber base. The secondary collection equipment, for example a bag
filter or air scrubber, is placed after the drying chamber. The choice of separation and
exhaust equipment depends on the product formed, that is, the number of fines
present, the heat sensitivity, stickiness and the collection equipment installed.

2.1.2 Effect of Spray Drying Variables on the Product
Manipulation of the spray drying characteristics can alter the final product
characteristics. Spray dried materials are usually spherical in shape with a narrow size
distribution and often hollow (Newton, 1966). A given material however, may be
spray dried to give different sizes, to be hollow, solid or agglomerated. The dryer
design, dimensions and operation is largely chosen according to the final product
required (Marshall and Seltzer, 1950b). For example if a dryer design is chosen to
produce a fine product it is very difficult to then product a coarse one.

Feed Concentration
Solutions prepared using hydrophilic materials increase in viscosity with an increase
in concentration. Spray drying of these materials usually results in powders with low
bulk density. An increase in concentration is accompanied by a decrease in bulk
density (Marshall and Seltzer, 1950b). With non hydrophilic materials an increase in
bulk density is generally accompanied by an increase in concentration (Marshall and
Seltzer, 1950b). Feed concentration influences the droplet size produced by the
atomiser, it is difficult therefore, to assess the individual effect on bulk density
(Marshall and Madison, 1955). Particle size generally decreases as feed concentration
decreases (Crosby and Marshall, 1958).
**Entrapped Air in Feed**

Trapped air or other non condensables in the feed tend to decrease the bulk density of the product. Air that is entrapped in the fluid may contribute to the formation of hollow gas filled particles (Marshall and Seltzer, 1950b). This fact is exploited in foam spray drying (Masters, 1990).

**Feed Temperature**

Increasing the temperature of the feed has two effects the first being, that there is a reduction in feed viscosity causing a decrease in droplet size produced by the atomiser (Marshall and Madison, 1955). Atomisation is made easier by the formation of droplets rather than "threads" (Masters, 1990). Secondly, the initial warm up period of drying is shortened and so the moisture content may be reduced slightly. Bulk density may be either increased or decreased depending on the effect on atomisation and the material involved, (Duffie and Marshall, 1953a). Marshall and Seltzer (1950b), however found that in general increasing the temperature of both hydrophilic and hydrophobic solutions was accompanied by a increase in bulk density. If an increase in feed temperature de-aerates the feed, a high bulk density can occur (Masters, 1990).

**Feed Rate**

An increase in feed rate increases the final moisture content in the product. The bulk density is also seen to increase, (Masters, 1990).

**Drying Air Temperature**

The temperature of the drying medium greatly influences bulk density and product shape. An increase in temperature promotes the "balloon forming" effect due the increase in pressure caused by the expanding moisture and vapour formation within the droplet, as mentioned above in the drying section (Marshall and Seltzer, 1950b). An increase in temperature also results in a greater evaporation, leading to a lower final moisture content (Chaloud et al. 1957). The particles size of certain materials
increase with an increase in air temperature due to the greater swelling and reduction in particle wall thickness (Duffie and Marshall, 1953b)

**Relative Direction of Air Flow**

Co-current air flow, as described earlier, produces predominately solid particles as a consequence of the wet particles encountering partially cooled, moist air during the drying process. Agglomeration is common with this type of air flow pattern, (Marshall and Seltzer, 1950b).

An increase in air throughput means that there is more air at the same inlet temperature. This results in a higher exhaust temperature and therefore, more total evaporation, a lower product moisture content and more steam vaporisation causing "ballooning" and hence a lower density, (Chaloud et al. 1957).

An increase in air turbulence causes an increase in relative velocity between the droplets and air so increasing the heat transfer coefficient leading to a higher drying rate. Faster drying leads to a cooling effect on the surrounding air causing lower vaporisation of the moisture with the drop, less expansion and therefore, higher density (Chaloud et al, 1957).

Although many of the variables can be altered to give desired product qualities the actual manipulation is very dependant on the spray dryer design and the material used.

### 2.1.3 Advantages and Disadvantages of Spray Drying

**Advantages**

i) The spray drying process can be manipulated to give a product with the desired physical properties, such as bulk density, particle size, moisture content and shape. These specifications can be maintained throughout the spray drying run regardless of
its length provided that the operating conditions are maintained. The variety of dryer
designs further increases the possibilities.

ii) Operation is simple and lends itself to full automation.

iii) Materials that are otherwise difficult to dry may be dried by spray drying. For
example, explosive materials that ignite when in contact with air may be dried by
using nitrogen, instead of air, as the drying gas. Materials that have strong odours
or that require sterile conditions may be dried using a closed system spray drier.
Spray drying is useful for the drying of heat sensitive materials. Evaporation rates are
fast and residual times are short, in the order of seconds. Materials that are spray
dried therefore do not actually reach the temperature of the surrounding air. Materials
such as pepsin and muscle extracts have been spray dried without any loss in enzymic

iv) Spray drying may be used for corrosive or abrasive feed stocks as long as they can
be pumped.

Disadvantages

i) Installation costs are high.

ii) The size of the industrial units are much larger per unit of product than other dryer
types. Also the physical size of the drying columns requires large housing buildings.

iii) Spray dryers have poor thermal efficiencies due to the fact that they are
convection dryers and hence are expensive to run.
2.2 Materials and Methods

2.2.1 Materials

Isoprenaline Hemisulfate salt.
Lot No. 127F-0171
Sigma Chemical Company, USA.

Isoprenaline Hydrochloride Salt
Lot No. 48C 0095
Sigma Chemical Company, USA.

Pentamidine Isethionate BP.
Batch No. RM/283/01
Rhône-Poulenc Rorer Ltd., Dagenham, London, UK.

Salbutamol Sulphate.
Micro Macinazone SA, Microgrinding Ltd., Switzerland.

Salbutamol Base.
Batch No. 1002.
Harris Pharmaceuticals Ltd., Patman House, George Lane, London, UK.

Conductive Carbon Cement.
Neubauer, W. Germany.

Cyclohexane, HPLC grade.
Aldrich Chemical Co., USA.

N-Heptane, Analytical Reagent.
BDH Chemicals Ltd., Poole, UK.
2.2.2 Spray Drying

The drugs: isoprenaline hydrochloride and sulphate, salbutamol base and sulphate and pentamidine isethionate, were initially investigated to find a suitable drug model on which carry out further tests (see Appendix 2 for chemical profiles). Solutions of the drugs were prepared at varying concentrations and spray dried, using a Büchi 190 mini spray dryer (Büchi Laboratory-Techniques Ltd., CH-9230 Flawil) (fig. 2.4), under several conditions. Figure 2.5 shows, in the form of a flow diagram, the spray drying process used. The spray drying conditions investigated for each drug, operating within what appeared to be the practical limits, are given in tables 2.1 -2.5. For each spray dried batch the percentage yield was calculated and the particle size measured.

<table>
<thead>
<tr>
<th>CONTROL</th>
<th>RANGE INVESTIGATED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug Concentration, (%w/v)</td>
<td>10.0</td>
</tr>
<tr>
<td>Aspirator</td>
<td>10</td>
</tr>
<tr>
<td>Pump, (ml min⁻¹)</td>
<td>5</td>
</tr>
<tr>
<td>Flow Indicator (compressed air flow rate),(NL/Min)</td>
<td>800</td>
</tr>
<tr>
<td>Heating Control</td>
<td>7-11</td>
</tr>
<tr>
<td>Inlet Temperature, (°C)</td>
<td>153-193</td>
</tr>
<tr>
<td>Outlet Temperature, (°C)</td>
<td>95-119</td>
</tr>
</tbody>
</table>

Table 2.1 Spray Drying Conditions Investigated for Isoprenaline Hydrochloride.
Chapter Two - Spray Drying

Control Range Investigated

<table>
<thead>
<tr>
<th>Control</th>
<th>Range Investigated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug Concentration, (% w/v)</td>
<td>1.0-20.0</td>
</tr>
<tr>
<td>Aspirator</td>
<td>10-20</td>
</tr>
<tr>
<td>Pump, (ml min⁻¹)</td>
<td>5-15</td>
</tr>
<tr>
<td>Flow Indicator (compressed air flow rate), (NI/h)</td>
<td>200-800</td>
</tr>
<tr>
<td>Heating Control</td>
<td>7-11</td>
</tr>
<tr>
<td>Inlet Temperature, (°C)</td>
<td>153-180</td>
</tr>
<tr>
<td>Outlet Temperature, (°C)</td>
<td>86-119</td>
</tr>
</tbody>
</table>

Table 2.2 Spray Drying Conditions Investigated for Isoprenaline Sulphate.

<table>
<thead>
<tr>
<th>Control</th>
<th>Range Investigated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug Concentration, (% w/v)</td>
<td>0.5-1.0</td>
</tr>
<tr>
<td>Aspirator</td>
<td>10-18</td>
</tr>
<tr>
<td>Pump, (ml min⁻¹)</td>
<td>5-15</td>
</tr>
<tr>
<td>Flow Indicator (compressed air flow rate), (NI/h)</td>
<td>800</td>
</tr>
<tr>
<td>Heating Control, (°C)</td>
<td>3-11.5</td>
</tr>
<tr>
<td>Inlet Temperature, (°C)</td>
<td>105-182</td>
</tr>
<tr>
<td>Outlet Temperature</td>
<td>55-128°C</td>
</tr>
</tbody>
</table>

Table 2.3 Spray Drying Conditions Investigated for Salbutamol Base.
Chapter Two - Spray Drying

### CONTROL RANGE INVESTIGATED

<table>
<thead>
<tr>
<th>CONTROL</th>
<th>RANGE INVESTIGATED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug Concentration, (%w/v)</td>
<td>1.0-25.0</td>
</tr>
<tr>
<td>Aspirator</td>
<td>10-18</td>
</tr>
<tr>
<td>Pump, (ml min⁻¹)</td>
<td>5-15</td>
</tr>
<tr>
<td>Flow Indicator (compressed air flow rate),(NI/min)</td>
<td>800</td>
</tr>
<tr>
<td>Heating Control</td>
<td>3-10</td>
</tr>
<tr>
<td>Inlet Temperature, (°C)</td>
<td>105-190</td>
</tr>
<tr>
<td>Outlet Temperature, (°C)</td>
<td>51-122</td>
</tr>
</tbody>
</table>

*Table 2.4 Spray Drying Conditions Investigated for Salbutamol Sulphate.*

### CONTROL RANGE INVESTIGATED

<table>
<thead>
<tr>
<th>CONTROL</th>
<th>RANGE INVESTIGATED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug Concentration, (%w/v)</td>
<td>1.0-10.0</td>
</tr>
<tr>
<td>Aspirator</td>
<td>10-20</td>
</tr>
<tr>
<td>Pump, (ml min⁻¹)</td>
<td>3-7</td>
</tr>
<tr>
<td>Flow Indicator (compressed air flow rate),(NI/min)</td>
<td>800</td>
</tr>
<tr>
<td>Heating Control</td>
<td>3-9</td>
</tr>
<tr>
<td>Inlet Temperature, (°C)</td>
<td>121-196</td>
</tr>
<tr>
<td>Outlet Temperature, (°C)</td>
<td>55-122</td>
</tr>
</tbody>
</table>

*Table 2.5 Spray Drying Conditions Investigated for Pentamidine Isethionate.*
Inlet Temperature Gauge

Pneumatic Nozzle

Drying Column

Feed Solution

Outlet Temperature Gauge

Collection Vessel

Figure 2.4 - Büchi 190 Mini Spray Dryer.
Figure 2.5 - Flow Diagram of the Spray Drying Process.
2.2.3 Measurement of Yield

Yield was calculated from the weight of the product collected, as a percentage of the initial quantity used in the feed solution. The weight of the product was calculated from the weight difference in the collection vessel, before and after spray drying. Weighings were made using a digital balance (Sartorius Ltd., Longmead Business Centre, Surrey, UK).

2.2.4 Particle Size Measurement

The spray dried product from each batch was sized by two techniques; visually by scanning electron microscopy and laser diffraction. Both spray dried and starting materials were sized.

Scanning Electron Microscopy (S.E.M)

A sample from each batch of spray dried product was mounted onto an aluminium stub by means of double sided sticky tape or by dusting onto a glass slide, which was then placed onto the stub using a high conducting carbon cement. In cases where only a small batch of material was spray dried, powders were spray dried directly onto the stub by placing the stub in the collection vessel of the spray dryer. S.E.M stubs were placed at various positions within the collection vessel (fig. 2.6), to determine whether the position had any effect on the sample collected.

![Figure 2.6 Stub Positions Investigated in the Spray Dryer Collection Vessel.](image-url)
Chapter Two - Spray Drying

Once mounted onto an aluminium stub, the samples were coated with a fine layer of gold using a sputter coater (Emitech K550) with a gold target, at 40 mA for 2-4 minutes and viewed under a Phillips XL20, (Phillips Analytical UK) scanning electron microscope, at an accelerating voltage of between 10-15 KV (fig. 2.7). The size and shape of individual particles could be determined from the scanning electron micrographs obtained.

**Laser Diffraction**

The particle size distribution of each batch was measured using a Malvern 2600C Lasersizer, (Malvern Ltd., UK). A collimated, monochromatic analyser beam, of about 1 cm in diameter is formed from a low power Helium-Neon laser. The light scattered by the suspension of particles in the beam path and the unscattered remainder are incident onto a receiver lens, also known as the range lens. The configuration of the range lens is such that the diffraction pattern of a particle, wherever it lies in the analyser beam is stationary and centred on the optical axis, even if the particle is moving. This lens acts as a Fourier Transform lens forming a far field diffraction pattern at is focal plane. At the focal plane the diffraction pattern is collected by a detector. The detector is special in that it comprises of 31 concentric rings.

The unscattered light is focused on the detector, passed through a small aperture in the detector and out of the optical system. The total laser power passing out of the system can thus be monitored and hence the sample volume concentration determined.

Particle size distributions are calculated using data collected over a period of time. At any one instant many particles are present in the analyser beam path and thus the scattered light measured is the sum of individual patterns overlaid on the central axis. As the material flows across the beam the scattered light pattern changes, it is these instantaneous changes that are recorded. Each detector recording is known as a sweep and the summation of these are used to calculate the size distribution.
Figure 2.7 Phillips XL20, Scanning Electron Microscope.
Chapter Two - Spray Drying

This method of analysis has the advantage that sufficient data is collected to preform statistically significant calculations and the bulk of the sample is adequately represented. The measurement is one of volume, based on the theory devised by Mie describing the diffraction of a plane monochromatic wave by a homogeneous sphere of any diameter. This is an expansion of the theory originally developed by Rayleigh, who showed that the scattered light intensity by a particle in a wavelength of light is proportional to the square of the volume of the particle and inversely proportional to the fourth power of the wavelength of light, (eqn. 2.5).

\[ S = 24\pi^3 \left( \frac{m^2-1}{m^2+2} \right) \frac{v^2}{\lambda^2} \]

\textit{Equation 2.5}

Where \( S \)=Scattered light, \( \lambda \)=Wavelength, \( v \)=Volume of sphere, \( m \)=Refractive index.

Particles are measured suspended in a suitable suspending medium, that is, one which is clear at a wavelength of 633 nm wavelength, optically homogeneous and does not interact with the sample to change its size. The particles should be easily dispersed without clumping or aggregating on the walls of the vessel. Heptane and cyclohexane were investigated as potential suspending media and a standard method developed for all other measurements. The effects of sonication, stirring and surfactant additions were studied.

The Malvern Lasersizer software was set to the model independent mode so the best fit size distribution to the data was always calculated. The printout obtained from the instrument indicates the size distribution, frequency, log difference (which gives an indication of the degree of fit to the distribution in question), the specific surface area, median particle size, 10% and 90% particle undersize values.
2.2.5 Photography of the Atomised Spray

An attempt was made to photograph the emerging atomised spray from the pneumatic nozzle. This was done in order to gain an idea of primary droplet size, using a non-invasive technique. The spray dryer was put into operation using water as the feed solution. The spray was highly illuminated using carbon source lighting and tungsten filament, 240 V angle poise lamps, (fig. 2.8). Photographs were taken using a high shutter speed camera at varying settings. A stroboscope was also employed in an attempt to "still" the spray whilst photographing.
Figure 2.8 Apparatus for Photographing Atomised Spray
from the Spray Dryer Nozzle.
2.3 Results

2.3.1 Scanning Electron Microscopy

When spray drying directly on to an aluminum stub, the stub position had no effect on the sample collected. When viewed under the scanning electron microscope the particle size was found to be constant regardless of the sampling position. The stub position used for subsequent experiments was the centre bottom of the collection vessel.

The best method for mounting, when larger batches of material were spray dried was found to be the use of double sided sticky tape to hold the powder sample onto the S.E.M stub. Care had to be taken to correctly coat the material with a thin layer of gold, once mounted on the stub. In some cases the particles were seen to be destroyed at longer coating times. In general therefore, materials were held on the aluminum stub using double sided sticky tape and coated with gold for a minimum time of two minutes.

2.3.2 Particle Sizing using Laser Diffraction

Cyclohexane was the best dispersant for determination of the particle size of all drugs investigated. When salbutamol sulphate was tapped directly into the measuring cell the median particle size was seen to decrease over a period of time, (table 2.6). When stirred for a minimum of three hours in the dispersant, the measured median particle size was seen to be more constant, (tables 2.7(a-g)). Sonication proved to be a more efficient method of dispersing the solid in the liquid, (table 2.8(a-e)). The spray dried salbutamol base used for these experiments, however, when viewed by the scanning electron microscope was found to be non spherical in shape. The decrease in particle size therefore is probably a function of deaggregation. When a spray dried material such as isoprenaline sulphate was analysed after first sonicating a little of the material in cyclohexane, the median particle size was seen to remain constant (table 2.9). The method adopted therefore, for subsequent size analysis was as follows: a little of the
powder was placed in approximately 10 ml of cyclohexane and sonicated for 30 seconds, a few drops of this suspension was then added to the Malvern cell, containing cyclohexane and sized immediately.

<table>
<thead>
<tr>
<th>Time in Malvern cell (min)</th>
<th>Median Particle Size (μm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>63.41</td>
</tr>
<tr>
<td>5</td>
<td>57.5</td>
</tr>
<tr>
<td>10</td>
<td>55.5</td>
</tr>
<tr>
<td>16</td>
<td>53.6</td>
</tr>
<tr>
<td>17</td>
<td>53.6</td>
</tr>
<tr>
<td>21</td>
<td>52.6</td>
</tr>
<tr>
<td>32</td>
<td>50.4</td>
</tr>
<tr>
<td>39</td>
<td>47.9</td>
</tr>
<tr>
<td>76</td>
<td>33.0</td>
</tr>
<tr>
<td>85</td>
<td>24.5</td>
</tr>
<tr>
<td>92</td>
<td>22.6</td>
</tr>
<tr>
<td>94</td>
<td>21.6</td>
</tr>
</tbody>
</table>

Table 2.6 The Effect of Time on the Median Particle Size of Spray Dried Salbutamol Base, Dispersed in Cyclohexane.
### Table 2.7a The Median Particle Size of Spray Dried Salbutamol Sulphate as a function of time. Sample stirred for half an hour before sizing.

<table>
<thead>
<tr>
<th>Time in Malvern Cell (min)</th>
<th>Median Particle Size ($\mu$m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>43.5</td>
</tr>
<tr>
<td>6</td>
<td>39.2</td>
</tr>
<tr>
<td>9</td>
<td>38.0</td>
</tr>
<tr>
<td>15</td>
<td>37.0</td>
</tr>
<tr>
<td>18</td>
<td>35.0</td>
</tr>
<tr>
<td>21</td>
<td>33.8</td>
</tr>
<tr>
<td>23</td>
<td>33.8</td>
</tr>
</tbody>
</table>

### Table 2.7b The Median Particle Size of Spray Dried Salbutamol Sulphate as a Function of Time. Sample stirred for one hour before sizing.

<table>
<thead>
<tr>
<th>Time in Malvern Cell (min)</th>
<th>Median Particle Size ($\mu$m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>28.8</td>
</tr>
<tr>
<td>3</td>
<td>28.9</td>
</tr>
<tr>
<td>9</td>
<td>28.2</td>
</tr>
<tr>
<td>39</td>
<td>26.5</td>
</tr>
<tr>
<td>54</td>
<td>25.7</td>
</tr>
</tbody>
</table>
### Table 2.7c The Median Particle Size of Spray Dried Salbutamol Sulphate as a Function of Time. Sample stirred for two hours before sizing.

<table>
<thead>
<tr>
<th>Time in Malvern Cell (min)</th>
<th>Median Particle Size (µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>19.3</td>
</tr>
<tr>
<td>4</td>
<td>19.5</td>
</tr>
<tr>
<td>7</td>
<td>19.2</td>
</tr>
<tr>
<td>14</td>
<td>18.3</td>
</tr>
<tr>
<td>22</td>
<td>17.5</td>
</tr>
<tr>
<td>23</td>
<td>17.3</td>
</tr>
<tr>
<td>45</td>
<td>14.4</td>
</tr>
<tr>
<td>49</td>
<td>13.9</td>
</tr>
</tbody>
</table>

### Table 2.7d The Median Particle Size of Spray Dried Salbutamol Sulphate as a Function of Time. Sample stirred for three hours before sizing.

<table>
<thead>
<tr>
<th>Time in Malvern Cell (min)</th>
<th>Median Particle Size (µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>12.5</td>
</tr>
<tr>
<td>3</td>
<td>12.8</td>
</tr>
<tr>
<td>39</td>
<td>13.1</td>
</tr>
<tr>
<td>55</td>
<td>12.9</td>
</tr>
</tbody>
</table>

*Table 2.7c The Median Particle Size of Spray Dried Salbutamol Sulphate as a Function of Time. Sample stirred for two hours before sizing.*

*Table 2.7d The Median Particle Size of Spray Dried Salbutamol Sulphate as a Function of Time. Sample stirred for three hours before sizing.*
### Chapter Two - Spray Drying

<table>
<thead>
<tr>
<th>Time in Malvern Cell (mins)</th>
<th>Median Particle Size (μm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>9.4</td>
</tr>
<tr>
<td>36</td>
<td>8.7</td>
</tr>
<tr>
<td>58</td>
<td>8.1</td>
</tr>
</tbody>
</table>

*Table 2.7e The Median Particle Size of Spray Dried Salbutamol Sulphate as a Function of time. Sample stirred for *four hours* before sizing.*

<table>
<thead>
<tr>
<th>Time in Malvern Cell (min)</th>
<th>Median Particle Size (μm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>8.4</td>
</tr>
<tr>
<td>4</td>
<td>7.6</td>
</tr>
<tr>
<td>10</td>
<td>7.4</td>
</tr>
</tbody>
</table>

*Table 2.7f The Median Particle Size of Spray Dried Salbutamol Sulphate as a Function of Time. Sample stirred for *five hours* before sizing.*

<table>
<thead>
<tr>
<th>Time in Malvern Cell (min)</th>
<th>Median Particle Size (μm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>7.8</td>
</tr>
<tr>
<td>3</td>
<td>7.3</td>
</tr>
<tr>
<td>4</td>
<td>7.2</td>
</tr>
<tr>
<td>7</td>
<td>7.1</td>
</tr>
<tr>
<td>10</td>
<td>7.0</td>
</tr>
</tbody>
</table>

*Table 2.7g The Median Particle Size of Spray Dried Salbutamol Sulphate as a Function of Time. Sample stirred for *five hours 15 minutes* before sizing.*
Chapter Two - Spray Drying

The effect of sonication on median particle size of spray dried salbutamol sulphate:

<table>
<thead>
<tr>
<th>Time in Malvern Cell (min)</th>
<th>Median Particle Size (μm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>18.2</td>
</tr>
<tr>
<td>5</td>
<td>15.7</td>
</tr>
<tr>
<td>7</td>
<td>15.2</td>
</tr>
<tr>
<td>8</td>
<td>14.8</td>
</tr>
</tbody>
</table>

*Table 2.8a The Median Particle Size of Spray Dried Salbutamol Sulphate as a Function of Time. Sample sonicated for 3 minutes before sizing.*

<table>
<thead>
<tr>
<th>Time in Malvern Cell (min)</th>
<th>Median Particle Size (μm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>17.8</td>
</tr>
<tr>
<td>8</td>
<td>13.8</td>
</tr>
<tr>
<td>9</td>
<td>13.7</td>
</tr>
<tr>
<td>11</td>
<td>13.4</td>
</tr>
<tr>
<td>13</td>
<td>13.0</td>
</tr>
<tr>
<td>15</td>
<td>12.9</td>
</tr>
</tbody>
</table>

*Table 2.8b The Median Particle Size of Spray Dried Salbutamol Sulphate as a Function of Time. Sample sonicated for 17 minutes before sizing.*
### Chapter Two - Spray Drying

<table>
<thead>
<tr>
<th>Time in Malvern Cell (min)</th>
<th>Median Particle Size (μm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>16.6</td>
</tr>
<tr>
<td>3</td>
<td>13.9</td>
</tr>
<tr>
<td>4</td>
<td>13.3</td>
</tr>
<tr>
<td>6</td>
<td>12.7</td>
</tr>
<tr>
<td>11</td>
<td>11.8</td>
</tr>
<tr>
<td>13</td>
<td>11.7</td>
</tr>
</tbody>
</table>

*Table 2.8c* The Median Particle Size of Spray Dried Salbutamol Sulphate as a Function of Time. Sample sonicated 39 minutes before sizing.

<table>
<thead>
<tr>
<th>Time in Malvern Cell (min)</th>
<th>Median Particle Size (μm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>18.1</td>
</tr>
<tr>
<td>3</td>
<td>15.1</td>
</tr>
<tr>
<td>5</td>
<td>14.6</td>
</tr>
<tr>
<td>7</td>
<td>14.3</td>
</tr>
<tr>
<td>9</td>
<td>14.1</td>
</tr>
<tr>
<td>12</td>
<td>13.7</td>
</tr>
<tr>
<td>14</td>
<td>13.7</td>
</tr>
</tbody>
</table>

*Table 2.8d* The Median Particle Size of Spray Dried Salbutamol Sulphate as a Function of Time. Sample sonicated for 57 minutes before sizing.
Chapter Two - Spray Drying

<table>
<thead>
<tr>
<th>Time in Malvern Cell (min)</th>
<th>Median Particle Size (μm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>29.8</td>
</tr>
<tr>
<td>3</td>
<td>24.1</td>
</tr>
<tr>
<td>6</td>
<td>18.8</td>
</tr>
<tr>
<td>7</td>
<td>17.7</td>
</tr>
<tr>
<td>9</td>
<td>16.9</td>
</tr>
<tr>
<td>11</td>
<td>16.8</td>
</tr>
<tr>
<td>14</td>
<td>16.2</td>
</tr>
</tbody>
</table>

Table 2.8e The Median Particle Size of Spray Dried Salbutamol Sulphate as a Function of Time. Sample sonicated for 78 minutes before sizing.

<table>
<thead>
<tr>
<th>Time in Malvern Cell (min)</th>
<th>Median Particle Size (μm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>4.9</td>
</tr>
<tr>
<td>11</td>
<td>4.9</td>
</tr>
<tr>
<td>19</td>
<td>4.9</td>
</tr>
<tr>
<td>20</td>
<td>4.9</td>
</tr>
<tr>
<td>27</td>
<td>5.0</td>
</tr>
<tr>
<td>31</td>
<td>4.9</td>
</tr>
</tbody>
</table>

Table 2.9 The Median Particle Size of Spray Dried Isoprenaline Sulphate as a Function of Time. Sample sonicated for a few seconds before sizing.
2.3.3 Spray Drying Results

Isoprenaline Hydrochloride

Successful spray drying of isoprenaline hydrochloride was difficult. It was found that when spray dried, the isoprenaline hydrochloride crystallised around the cyclone area of the drier. The only yield obtained was that collected on the S.E.M. stub. The electron micrographs showed that individual particles were not formed on drying and after several days the powder collected on the stub was seen to crystallise due to moisture uptake, isoprenaline hydrochloride having a high water solubility (1 in less than 1 of water). The results from the spray drying conditions investigated are given in table 2.10.

Isoprenaline Sulphate

S.E.M indicated that on spray drying the isoprenaline sulphate powder changed from crystalline to individual spherical particles, (plates 2.1 and 2.2).

The results from the spray drying of isoprenaline sulphate are given in tables 2.11 to 2.15 and summarised graphically in figs 2.9 to 2.14. Median particle sizes, measured by laser diffraction, ranged from 4.1 to 8.9 µm. The scanning electron micrographs, however, indicated sizes of less than 1 µm to 5 µm. Percentage yields ranged from between 4% to 38%. An increase in the pump rate was accompanied by a decrease in outlet temperature and particle size, the latter could be due to a greater cooling of the surrounding air and hence less vapourisation of the internal moisture resulting in smaller, denser particles. An increase in feed concentration caused an increase in particle size, which would be expected as more material is present in each droplet. A decrease in spray flow rate, the quantity of compressed air, caused a reduction in the percentage yield. Further reduction resulted in a wet product, this would be expected as there would be too little compressed air to atomise the feed sufficiently, resulting in a larger droplet size and hence insufficient evaporation.
<table>
<thead>
<tr>
<th>Lot No.</th>
<th>Feed Conc. %w/v</th>
<th>Spray Flow level NI/h</th>
<th>Aspirator Level</th>
<th>Pump Level</th>
<th>Heating control level</th>
<th>Inlet Temp. °C</th>
<th>Outlet Temp. °C</th>
<th>Median Particle size, µm</th>
<th>Largest particle size from SEM, µm</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISCH3</td>
<td>10</td>
<td>800</td>
<td>10</td>
<td>5</td>
<td>7</td>
<td>153</td>
<td>95</td>
<td>90</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ISCH1</td>
<td>10</td>
<td>800</td>
<td>10</td>
<td>5</td>
<td>9</td>
<td>180</td>
<td>119</td>
<td>-</td>
<td>-</td>
<td>0.6</td>
</tr>
<tr>
<td>ISCH2</td>
<td>10</td>
<td>800</td>
<td>10</td>
<td>5</td>
<td>11</td>
<td>193</td>
<td>133</td>
<td>-</td>
<td>-</td>
<td>0.2</td>
</tr>
</tbody>
</table>

*Table 2.10 Spray Drying of Isoprenaline Hydrochloride.*
Plate 2.1 Isoprenaline Sulphate, Starting Material.

Plate 2.2 Isoprenaline Sulphate, Spray Dried Material.
<table>
<thead>
<tr>
<th>Lot No.</th>
<th>Feed Conc. %w/v</th>
<th>Spray Flow Level NI/h</th>
<th>Aspirator Level</th>
<th>Pump Level</th>
<th>Heating control level</th>
<th>Inlet Temp. °C</th>
<th>Outlet Temp. °C</th>
<th>Median Particle size, μm</th>
<th>Largest particle size from SEM, μm</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISO1</td>
<td>9</td>
<td>800</td>
<td>10</td>
<td>5</td>
<td>7</td>
<td>160</td>
<td>101</td>
<td>4.9</td>
<td>-</td>
<td>30</td>
</tr>
<tr>
<td>ISO2</td>
<td>9</td>
<td>800</td>
<td>10</td>
<td>5</td>
<td>7</td>
<td>160</td>
<td>101</td>
<td>5.0</td>
<td>2.0</td>
<td>21</td>
</tr>
<tr>
<td>ISO13</td>
<td>10</td>
<td>800</td>
<td>10</td>
<td>5</td>
<td>7</td>
<td>153</td>
<td>113</td>
<td>6.9</td>
<td>1.5</td>
<td>19</td>
</tr>
<tr>
<td>ISO3</td>
<td>10</td>
<td>800</td>
<td>10</td>
<td>5</td>
<td>9</td>
<td>180</td>
<td>120</td>
<td>6.5</td>
<td>6.5</td>
<td>28</td>
</tr>
<tr>
<td>ISO4</td>
<td>10</td>
<td>800</td>
<td>10</td>
<td>5</td>
<td>9</td>
<td>180</td>
<td>105</td>
<td>5.8</td>
<td>2.0</td>
<td>6.0</td>
</tr>
<tr>
<td>ISO5</td>
<td>10</td>
<td>800</td>
<td>10</td>
<td>5</td>
<td>11</td>
<td>195</td>
<td>116</td>
<td>-</td>
<td>1.0</td>
<td>24</td>
</tr>
<tr>
<td>ISO18</td>
<td>10.6</td>
<td>800</td>
<td>10</td>
<td>5</td>
<td>8</td>
<td>166</td>
<td>114</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 2.11 The Effect of Heating Control Level on Spray Drying of Isoprenaline Sulphate.
<table>
<thead>
<tr>
<th>Lot No.</th>
<th>Feed Conc. %w/v</th>
<th>Flow Indicator NI/h</th>
<th>Aspirator Level</th>
<th>Pump Level</th>
<th>Heating control level</th>
<th>Inlet Temp. °C</th>
<th>Outlet Temp. °C</th>
<th>Median Particle size, μm</th>
<th>Largest particle size from SEM, μm</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISO13</td>
<td>10</td>
<td>800</td>
<td>10</td>
<td>5</td>
<td>8</td>
<td>153</td>
<td>113</td>
<td>6.9</td>
<td>1.5</td>
<td>19</td>
</tr>
<tr>
<td>ISO6</td>
<td>10</td>
<td>800</td>
<td>10</td>
<td>10</td>
<td>7</td>
<td>160</td>
<td>86</td>
<td>5.3</td>
<td>-</td>
<td>39</td>
</tr>
<tr>
<td>ISO7</td>
<td>10</td>
<td>800</td>
<td>10</td>
<td>15</td>
<td>7</td>
<td>160</td>
<td>99</td>
<td>5.0</td>
<td>3.0</td>
<td>23</td>
</tr>
</tbody>
</table>

Table 2.12 The Effect of Pump Rate on the Spray Drying of Isoprenaline Sulphate.

<table>
<thead>
<tr>
<th>Lot No.</th>
<th>Feed Conc. %w/v</th>
<th>Spray Flow Level NI/h</th>
<th>Aspirator Level</th>
<th>Pump Level</th>
<th>Heating control level</th>
<th>Inlet Temp. °C</th>
<th>Outlet Temp. °C</th>
<th>Median Particle size, μm</th>
<th>Largest particle size from SEM, μm</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISO13</td>
<td>10</td>
<td>800</td>
<td>10</td>
<td>5</td>
<td>7</td>
<td>153</td>
<td>113</td>
<td>6.9</td>
<td>1.5</td>
<td>19</td>
</tr>
<tr>
<td>ISO8</td>
<td>10</td>
<td>800</td>
<td>15</td>
<td>5</td>
<td>7</td>
<td>160</td>
<td>124</td>
<td>4.1</td>
<td>3.0</td>
<td>24</td>
</tr>
<tr>
<td>ISO9</td>
<td>10</td>
<td>800</td>
<td>20</td>
<td>5</td>
<td>7</td>
<td>160</td>
<td>110</td>
<td>4.6</td>
<td>2.0</td>
<td>10</td>
</tr>
</tbody>
</table>

Table 2.13 The Effect of the Aspirator Level on the Spray Drying of Isoprenaline Sulphate.
<table>
<thead>
<tr>
<th>Lot No.</th>
<th>Feed Conc. %w/v</th>
<th>Spray Flow Level NI/h</th>
<th>Aspirator Level</th>
<th>Pump Level</th>
<th>Heating control level</th>
<th>Inlet Temp. °C</th>
<th>Outlet Temp. °C</th>
<th>Median Particle size, μm</th>
<th>Largest particle size from SEM, μm</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISO11</td>
<td>1.0</td>
<td>800</td>
<td>15</td>
<td>5</td>
<td>7</td>
<td>152</td>
<td>107</td>
<td>5.1</td>
<td>1.0</td>
<td>19</td>
</tr>
<tr>
<td>ISO10</td>
<td>5.0</td>
<td>800</td>
<td>15</td>
<td>5</td>
<td>7</td>
<td>152</td>
<td>108</td>
<td>4.5</td>
<td>1.2</td>
<td>31</td>
</tr>
<tr>
<td>ISO8</td>
<td>10.0</td>
<td>800</td>
<td>15</td>
<td>5</td>
<td>7</td>
<td>158</td>
<td>124</td>
<td>4.1</td>
<td>3.0</td>
<td>24</td>
</tr>
<tr>
<td>ISO12</td>
<td>20.0</td>
<td>800</td>
<td>15</td>
<td>5</td>
<td>7</td>
<td>154</td>
<td>112</td>
<td>8.9</td>
<td>2.2</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 2.14  The Effect of Feed Concentration on Spray Drying of Isoprenaline Sulphate.
<table>
<thead>
<tr>
<th>Lot No.</th>
<th>Feed Conc. %w/v</th>
<th>Spray Flow Level Nl/h</th>
<th>Aspirator Level</th>
<th>Pump Level</th>
<th>Heating control level</th>
<th>Inlet Temp. °C</th>
<th>Outlet Temp. °C</th>
<th>Median Particle size, μm</th>
<th>Largest particle size from SEM, μm</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISO8</td>
<td>10</td>
<td>800</td>
<td>15</td>
<td>5</td>
<td>7</td>
<td>158</td>
<td>124</td>
<td>4.1</td>
<td>3.0</td>
<td>24</td>
</tr>
<tr>
<td>ISO16</td>
<td>10</td>
<td>400</td>
<td>15</td>
<td>5</td>
<td>7</td>
<td>150</td>
<td>112</td>
<td>-</td>
<td>-</td>
<td>18</td>
</tr>
<tr>
<td>ISO14</td>
<td>10</td>
<td>200</td>
<td>15</td>
<td>5</td>
<td>7</td>
<td>156</td>
<td>113</td>
<td>-</td>
<td>-</td>
<td>8</td>
</tr>
<tr>
<td>ISO15</td>
<td>10</td>
<td>100</td>
<td>15</td>
<td>5</td>
<td>7</td>
<td>158</td>
<td>119</td>
<td>-</td>
<td>-</td>
<td>4</td>
</tr>
</tbody>
</table>

*Table 2.15 The Effect of Spray Flow Level (Quantity of pressurised air) on Spray Drying of Isoprenaline Sulphate.*
Chapter Two - Spray Drying

Figure 2.9 The Effect of Temperature Control Level on Percentage Yield of Spray Dried Isoprenaline Sulphate.

Figure 2.10 The Effect of Pump Speed on the Percentage Yield of Spray Dried Isoprenaline Sulphate.
Chapter Two - Spray Drying

Figure 2.11 The Effect of Pump Rate on the Median Particle Size of Spray Dried Isoprenaline Sulphate.

Figure 2.12 The Effect of Spray Flow (quantity of pressurised air) on the Percentage Yield of Isoprenaline Sulphate.
Chapter Two - Spray Drying

Figure 2.13 The Effect of Feed Concentration on the Percentage Yield of Spray Dried Isoprenaline Sulphate.

Figure 2.14 The Effect of Feed Concentration on the Median Particle Size of Spray Dried Isoprenaline Sulphate.
Chapter Two - Spray Drying

The particle size was seen to vary only slightly with changes in spray drying conditions, the above trends therefore, may not be significant. The optimum conditions which produced a product with a size of less than 5 μm with a reasonable yield, were found to be; compressed air flow 800 NI h⁻¹; Aspirator level 10; pump level 5 ml min⁻¹; heating control 7 (inlet temperature 150-160°C and outlet temperature 124-130°C).

Salbutamol Base

Results obtained from the spray drying of salbutamol base are summarised in tables 2.16 - 2.19. Yields were small, between 0.4% and 14%, this is probably a result of the poor solubility of salbutamol base (1 in 70), dictating low feed concentrations, (an increase in yield is usually observed with an increase in feed concentration, see section 2.1.2). Most of the powder product was carried out through the exhaust. Lowering the concentration resulted in a decrease in the yield to the point where the only yield collected was that on the S.E.M. stub. Increasing the pump rate to above 10 ml min⁻¹ resulted in too much moisture being present in the dryer to allow adequate evaporation and hence wet products. Slightly higher yields were seen at higher temperatures, but at very high temperatures (around 200°C) the salbutamol decomposed leaving a yellow residue on the glass surfaces of the spray dryer. At the higher temperatures the particles observed were not individual spheres but large bubbled particles. Lowering the inlet temperature improved the shape of the final product, that is, spherical particles were observed at lower inlet temperatures. Plates 2.3 and 2.4 show the change in particle size and shape observed when spray drying salbutamol. The best conditions for the spray drying of salbutamol base were found to be; compressed air flow rate 800 NI h⁻¹; pump rate 5 ml min⁻¹; aspirator level 18; heating control level 3 (inlet temperature 130°C and outlet temperature 70°C).
Plate 2.3  *Salbutamol Base, Starting Material.*

Plate 2.4  *Salbutamol Base, Spray Dried Material.*
<table>
<thead>
<tr>
<th>Lot No.</th>
<th>Feed Conc.</th>
<th>Spray Flow Level</th>
<th>Aspirator Level</th>
<th>Pump Level</th>
<th>Heating control level</th>
<th>Inlet Temp. °C</th>
<th>Outlet Temp. °C</th>
<th>Median Particle size, µm</th>
<th>Largest particle size from SEM, µm</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>S15</td>
<td>0.8</td>
<td>800</td>
<td>10</td>
<td>5</td>
<td>5</td>
<td>130</td>
<td>85</td>
<td>-</td>
<td>2</td>
<td>2.9</td>
</tr>
<tr>
<td>S19</td>
<td>0.8</td>
<td>800</td>
<td>10</td>
<td>5</td>
<td>5</td>
<td>134</td>
<td>67</td>
<td>-</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>S2</td>
<td>0.8</td>
<td>800</td>
<td>10</td>
<td>5</td>
<td>8</td>
<td>170</td>
<td>103</td>
<td>51.4</td>
<td>Not Spherical</td>
<td>12.7</td>
</tr>
<tr>
<td>S3</td>
<td>0.8</td>
<td>800</td>
<td>10</td>
<td>5</td>
<td>8</td>
<td>170</td>
<td>95</td>
<td>43.7</td>
<td>Not Spherical</td>
<td>9.0</td>
</tr>
<tr>
<td>S4</td>
<td>0.8</td>
<td>800</td>
<td>10</td>
<td>5</td>
<td>9</td>
<td>180</td>
<td>103</td>
<td>35.2</td>
<td>-</td>
<td>13.0</td>
</tr>
<tr>
<td>S5</td>
<td>0.8</td>
<td>800</td>
<td>10</td>
<td>5</td>
<td>9</td>
<td>180</td>
<td>106</td>
<td>49.2</td>
<td>-</td>
<td>11.0</td>
</tr>
<tr>
<td>S6</td>
<td>0.8</td>
<td>800</td>
<td>10</td>
<td>5</td>
<td>9</td>
<td>184</td>
<td>111</td>
<td>37.1</td>
<td>-</td>
<td>7.0</td>
</tr>
<tr>
<td>S8</td>
<td>0.8</td>
<td>800</td>
<td>10</td>
<td>5</td>
<td>11.5</td>
<td>200</td>
<td>126</td>
<td>-</td>
<td>-</td>
<td>5.0</td>
</tr>
</tbody>
</table>

Table 2.16 The Effect of the Heating Control Level on Spray drying of Salbutamol Base.
<table>
<thead>
<tr>
<th>Lot No.</th>
<th>Feed Conc. %w/v</th>
<th>Spray Flow Level NI/h</th>
<th>Aspirator Level</th>
<th>Pump Level</th>
<th>Heating control level</th>
<th>Inlet Temp. ºC</th>
<th>Outlet Temp. ºC</th>
<th>Median Particle size, µm</th>
<th>Largest particle size from SEM, µm</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>S17</td>
<td>1.0</td>
<td>800</td>
<td>10</td>
<td>5</td>
<td>9</td>
<td>182</td>
<td>94</td>
<td>-</td>
<td>-</td>
<td>5.0</td>
</tr>
<tr>
<td>S11</td>
<td>0.8</td>
<td>800</td>
<td>10</td>
<td>10</td>
<td>9</td>
<td>180</td>
<td>102</td>
<td>-</td>
<td>Not Spherical</td>
<td>14.0</td>
</tr>
<tr>
<td>S12</td>
<td>0.8</td>
<td>800</td>
<td>10</td>
<td>10</td>
<td>9</td>
<td>180</td>
<td>115</td>
<td>-</td>
<td>Not Spherical</td>
<td>-</td>
</tr>
<tr>
<td>S38</td>
<td>0.8</td>
<td>800</td>
<td>10</td>
<td>10</td>
<td>9</td>
<td>180</td>
<td>65</td>
<td>-</td>
<td>Not Spherical</td>
<td>0.2</td>
</tr>
<tr>
<td>S40</td>
<td>0.8</td>
<td>800</td>
<td>10</td>
<td>15</td>
<td>9</td>
<td>180</td>
<td>70</td>
<td>-</td>
<td>-</td>
<td>Wet Product</td>
</tr>
<tr>
<td>S25b</td>
<td>0.8</td>
<td>800</td>
<td>18</td>
<td>3</td>
<td>5</td>
<td>125</td>
<td>61</td>
<td>-</td>
<td>Not Spherical</td>
<td>0.9</td>
</tr>
<tr>
<td>S46</td>
<td>0.8</td>
<td>800</td>
<td>18</td>
<td>7</td>
<td>5</td>
<td>135</td>
<td>63</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>S26</td>
<td>0.8</td>
<td>800</td>
<td>18</td>
<td>10</td>
<td>5</td>
<td>135</td>
<td>98</td>
<td>-</td>
<td>-</td>
<td>Wet product</td>
</tr>
</tbody>
</table>

Table 2.17 The Effect of Pump Rate on Spray Drying of Salbutamol Base.
<table>
<thead>
<tr>
<th>Lot No.</th>
<th>Feed Conc. %w/v</th>
<th>Spray Flow Level NI/h</th>
<th>Aspirator Level</th>
<th>Pump Level</th>
<th>Heating control level</th>
<th>Inlet Temp. °C</th>
<th>Outlet Temp. °C</th>
<th>Median Particle size, μm</th>
<th>Largest particle size from SEM, μm</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>S11</td>
<td>0.8</td>
<td>800</td>
<td>10</td>
<td>10</td>
<td>9</td>
<td>180</td>
<td>102</td>
<td>-</td>
<td>Not Spherical</td>
<td>14.0</td>
</tr>
<tr>
<td>S12</td>
<td>0.8</td>
<td>800</td>
<td>10</td>
<td>10</td>
<td>9</td>
<td>180</td>
<td>115</td>
<td>-</td>
<td>Not Spherical</td>
<td>-</td>
</tr>
<tr>
<td>S13</td>
<td>0.9</td>
<td>800</td>
<td>15</td>
<td>10</td>
<td>9</td>
<td>180</td>
<td>111</td>
<td>-</td>
<td>-</td>
<td>9.04</td>
</tr>
<tr>
<td>S14</td>
<td>0.8</td>
<td>800</td>
<td>15</td>
<td>10</td>
<td>9</td>
<td>180</td>
<td>97</td>
<td>-</td>
<td>Not Spherical</td>
<td>10.0</td>
</tr>
<tr>
<td>S39</td>
<td>0.8</td>
<td>800</td>
<td>18</td>
<td>10</td>
<td>9</td>
<td>180</td>
<td>122</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 2.18 *The Effect of Aspirator Level on Spray Drying of Salbutamol Base.*
Table 2.19 The Effect of Feed Concentration on Spray Drying of Salbutamol Base.
Salbutamol Sulphate

On spray drying, the salbutamol sulphate was seen to alter in physical appearance, (plates 2.5 and 2.6). The particles produced were generally spherical, occasionally with pitted surfaces. Generally yields increased with rises in inlet temperature, (table 2.20 and fig. 2.15). Decreasing the feed concentration decreased the yield and particle size of the powder, (table 2.22, fig. 2.15 and fig. 2.16). With a decrease in size and consequently an increase in fines, more of the product was carried out with the exhaust air. The yields obtained ranged from 0.8% to 42%. The aspirator control level had little effect on particle size. A very slight increase in yield occurred with an increase in aspirator level, (table 2.21). The best conditions for the spray drying of salbutamol sulphate were found to be; air flow level 800 NI h⁻¹; aspirator level 18; pump rate 5 ml min⁻¹; heating control level, 7 (inlet temperature 160°C and outlet temperature 120°C).

Pentamidine Isethionate

Spray drying of pentamidine isethionate did not produce powders of individual, spherical particles, under the conditions investigated, (plates 2.7 and 2.8).
Plate 2.5 Salbutamol Sulphate, Starting Material

Plate 2.6 Salbutamol Sulphate, Spray Dried Material.
<table>
<thead>
<tr>
<th>Lot No.</th>
<th>Feed Conc. % w/v</th>
<th>Spray Flow Level NL/h</th>
<th>Aspirator Level</th>
<th>Pump Level</th>
<th>Heating control level</th>
<th>Inlet Temp. °C</th>
<th>Outlet Temp. °C</th>
<th>Median Particle size, μm</th>
<th>Largest particle size from SEM, μm</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>SS11</td>
<td>10</td>
<td>800</td>
<td>10</td>
<td>5</td>
<td>3</td>
<td>106</td>
<td>51</td>
<td>6.9</td>
<td>4.0</td>
<td>25</td>
</tr>
<tr>
<td>SS7</td>
<td>10</td>
<td>800</td>
<td>10</td>
<td>5</td>
<td>5</td>
<td>130</td>
<td>77</td>
<td>4.6</td>
<td>-</td>
<td>54.0</td>
</tr>
<tr>
<td>SS9</td>
<td>10</td>
<td>800</td>
<td>10</td>
<td>5</td>
<td>5</td>
<td>135</td>
<td>91</td>
<td>7.1</td>
<td>4.0</td>
<td>30.</td>
</tr>
<tr>
<td>SS12</td>
<td>10</td>
<td>800</td>
<td>10</td>
<td>5</td>
<td>7</td>
<td>160</td>
<td>83</td>
<td>5.9</td>
<td>-</td>
<td>23.0</td>
</tr>
<tr>
<td>SS4</td>
<td>10</td>
<td>800</td>
<td>10</td>
<td>5</td>
<td>8</td>
<td>168</td>
<td>106</td>
<td>5.2</td>
<td>Not individual particles</td>
<td>53.0</td>
</tr>
<tr>
<td>SS2</td>
<td>10</td>
<td>800</td>
<td>10</td>
<td>5</td>
<td>9</td>
<td>178</td>
<td>120</td>
<td>6.2</td>
<td>3.0</td>
<td>26.0</td>
</tr>
<tr>
<td>SS8</td>
<td>10</td>
<td>800</td>
<td>10</td>
<td>5</td>
<td>9</td>
<td>180</td>
<td>121</td>
<td>6.1</td>
<td>3.0</td>
<td>43.0</td>
</tr>
<tr>
<td>SS3</td>
<td>10</td>
<td>800</td>
<td>10</td>
<td>5</td>
<td>10</td>
<td>180</td>
<td>104</td>
<td>5.8</td>
<td>3.0</td>
<td>27.0</td>
</tr>
</tbody>
</table>

Table 2.20 The Effect of the Heating Control Level on Spray Drying of Salbutamol Sulphate.
<table>
<thead>
<tr>
<th>Lot No.</th>
<th>Feed Conc. %w/v</th>
<th>Flow Indicator NI/L</th>
<th>Aspirator Level</th>
<th>Pump Level</th>
<th>Heating control level</th>
<th>Inlet Temp. °C</th>
<th>Outlet Temp. °C</th>
<th>Median Particle size, μm</th>
<th>Largest particle size from SEM, μm</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>SS4</td>
<td>10</td>
<td>800</td>
<td>10</td>
<td>5</td>
<td>8</td>
<td>168</td>
<td>106</td>
<td>5.2</td>
<td>Particles not individual</td>
<td>35.0</td>
</tr>
<tr>
<td>SSI</td>
<td>10</td>
<td>800</td>
<td>15</td>
<td>5</td>
<td>8</td>
<td>163</td>
<td>122</td>
<td>5.6</td>
<td>3.0</td>
<td>32.0</td>
</tr>
<tr>
<td>SS13</td>
<td>10</td>
<td>800</td>
<td>18</td>
<td>5</td>
<td>8</td>
<td>165</td>
<td>95</td>
<td>5.3</td>
<td>5.0</td>
<td>30.0</td>
</tr>
<tr>
<td>SS5</td>
<td>10</td>
<td>800</td>
<td>20</td>
<td>5</td>
<td>8</td>
<td>166</td>
<td>113</td>
<td>6.6</td>
<td>3.0</td>
<td>48.0</td>
</tr>
</tbody>
</table>

*Table 2.21 The Effect of Aspirator Level on Spray Drying of Salbutamol Sulphate.*
<table>
<thead>
<tr>
<th>Lot No.</th>
<th>Feed Conc. %w/v</th>
<th>Spray Flow Level NI/h</th>
<th>Aspirator Level</th>
<th>Pump Level</th>
<th>Heating control level</th>
<th>Inlet Temp. °C</th>
<th>Outlet Temp. °C</th>
<th>Median Particle size, μm</th>
<th>Largest particle size from SEM, μm</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>SS23</td>
<td>1.0</td>
<td>800</td>
<td>18</td>
<td>5</td>
<td>5</td>
<td>129</td>
<td>72</td>
<td>5.5</td>
<td>2.0</td>
<td>11.0</td>
</tr>
<tr>
<td>SS25</td>
<td>1.0</td>
<td>800</td>
<td>18</td>
<td>5</td>
<td>5</td>
<td>130</td>
<td>70</td>
<td>9.0</td>
<td>3.0</td>
<td>16.0</td>
</tr>
<tr>
<td>SS18</td>
<td>5.0</td>
<td>800</td>
<td>18</td>
<td>5</td>
<td>5</td>
<td>130</td>
<td>73</td>
<td>-</td>
<td>3.0</td>
<td>28.0</td>
</tr>
<tr>
<td>SS9</td>
<td>10.0</td>
<td>800</td>
<td>10</td>
<td>5</td>
<td>5</td>
<td>135</td>
<td>91</td>
<td>7.1</td>
<td>4.0</td>
<td>30.0</td>
</tr>
<tr>
<td>SS40</td>
<td>20.0</td>
<td>800</td>
<td>10</td>
<td>5</td>
<td>5</td>
<td>140</td>
<td>60</td>
<td>4.6</td>
<td>2.0</td>
<td>27.0</td>
</tr>
<tr>
<td>SS29</td>
<td>25.0</td>
<td>800</td>
<td>18</td>
<td>5</td>
<td>5</td>
<td>135</td>
<td>98</td>
<td>6.2</td>
<td>3.0</td>
<td>32.0</td>
</tr>
</tbody>
</table>

*Table 2.22 The Effect of feed Concentration on Spray Drying of Salbutamol Sulphate.*
Chapter Two - Spray Drying

Figure 2.15 The Effect of Heating Control Level on the Particle Size of Spray Dried Salbutamol Sulphate at Different Feed Concentrations.

Figure 2.16 The Effect of Heating Control Level on the Percentage Yield of Spray Dried Salbutamol Sulphate at Different Feed Concentrations.

Where 1 = 5% w/v, 2 = 10% w/v and 3 = 25% w/v
Plate 2.7 Pentamidine Isethionate, Starting Material.

Plate 2.8 Pentamidine Isethionate, Spray Dried Material.
Manipulation of the spray drying parameters used however did alter the physical appearance of the powders, plate 2.9, shows pentamidine isethionate, spray dried under the following conditions; aspirator level 18; compressed air flow rate 800 NI h⁻¹; pump rate 3 ml min⁻¹ and heat control level, 8 (inlet temperature 180°C and outlet temperature 114°C). The results from the range of conditions investigated are summarised in tables 2.23 to 2.25. Percentage yields, ranging from 0 to 62%, are higher than those of previous drugs investigated and increased with an increase in inlet temperature, (table 2.23) and also by an increase in feed concentration, (table 2.25). Powders became more spherical in shape as the pump rate was decreased, the feed concentration lowered and the aspirator level increased.

2.3.4 Photography of the Atomised Spray

The photographs obtained, from the high speed photography of the atomised spray as it emerged from the nozzle, did not show the spray in sufficient detail for the droplet size to be determined. There were several problems with the method used; firstly the spray was so fine that the actual droplets were approaching the size of the grain of the photographic paper and secondly the spray travelled at a very high speed which was not stilled by the use of a stroboscope. The best pictures were found to be taken under the following conditions; 1600 ASA black and white film (Ilford XP1), a shutter speed of four thousandths of a second with tungsten external lighting, using a 70 mm macro lens and an aperture of 3.3 (plate 2.10).
Plate 2.9  Pentamidine Isethionate, Spray Dried Material, Lot pen 9.
<table>
<thead>
<tr>
<th>Lot No.</th>
<th>Feed Conc. %w/v</th>
<th>Spray Flow Level NI/h</th>
<th>Aspirator Level</th>
<th>Pump Level</th>
<th>Heating control level</th>
<th>Inlet Temp. °C</th>
<th>Outlet Temp. °C</th>
<th>Median Particle size, µm</th>
<th>Largest particle size from SEM, µm</th>
<th>% Yield</th>
<th>Sphericity</th>
</tr>
</thead>
<tbody>
<tr>
<td>P5</td>
<td>5</td>
<td>800</td>
<td>15</td>
<td>5</td>
<td>3</td>
<td>121</td>
<td>55</td>
<td>56.5</td>
<td>Not Spherical</td>
<td>47.0</td>
<td></td>
</tr>
<tr>
<td>P1</td>
<td>5</td>
<td>800</td>
<td>15</td>
<td>5</td>
<td>5</td>
<td>134</td>
<td>73</td>
<td>4.2</td>
<td>Not Spherical</td>
<td>32.0</td>
<td></td>
</tr>
<tr>
<td>P2</td>
<td>5</td>
<td>800</td>
<td>15</td>
<td>5</td>
<td>5</td>
<td>134</td>
<td>73</td>
<td>60</td>
<td>Not Spherical</td>
<td>39.0</td>
<td></td>
</tr>
<tr>
<td>P3</td>
<td>5</td>
<td>800</td>
<td>15</td>
<td>5</td>
<td>7</td>
<td>154</td>
<td>85</td>
<td>54.5</td>
<td>Not Spherical</td>
<td>35.0</td>
<td></td>
</tr>
<tr>
<td>P4</td>
<td>5</td>
<td>800</td>
<td>15</td>
<td>5</td>
<td>9</td>
<td>182</td>
<td>100</td>
<td>63.1</td>
<td>Not Spherical</td>
<td>32.0</td>
<td></td>
</tr>
</tbody>
</table>

*Table 2.23 The Effect of the Heat Control Level on Spray Drying of Pentamidine Isethionate.*
<table>
<thead>
<tr>
<th>Lot No.</th>
<th>Feed Conc. %w/v</th>
<th>Spray Flow Level NI/h</th>
<th>Aspirator Level</th>
<th>Pump Level</th>
<th>Heating control level</th>
<th>Inlet Temp. °C</th>
<th>Outlet Temp. °C</th>
<th>Median Particle size, µm</th>
<th>Largest particle size from SEM, µm</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>5</td>
<td>800</td>
<td>15</td>
<td>5</td>
<td>5</td>
<td>134</td>
<td>73</td>
<td>4.2</td>
<td>Not Spherical</td>
<td>32.0</td>
</tr>
<tr>
<td>PEN5</td>
<td>5</td>
<td>800</td>
<td>18</td>
<td>5</td>
<td>8</td>
<td>183</td>
<td>101</td>
<td>-</td>
<td>Not Spherical</td>
<td>-</td>
</tr>
<tr>
<td>P6</td>
<td>5</td>
<td>800</td>
<td>20</td>
<td>5</td>
<td>5</td>
<td>132</td>
<td>70</td>
<td>64.3</td>
<td>Not Spherical</td>
<td>29.0</td>
</tr>
</tbody>
</table>

*Table 2.24 The Effect of the Aspirator Level on Spray Drying of Pentamidine Isethionate.*
<table>
<thead>
<tr>
<th>Lot No.</th>
<th>Feed Conc. % w/v</th>
<th>Spray Flow Level NI/h</th>
<th>Aspirator Level</th>
<th>Pump Level</th>
<th>Heating control level</th>
<th>Inlet Temp. °C</th>
<th>Outlet Temp. °C</th>
<th>Largest particle size from SEM, μm</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEN9</td>
<td>1.0</td>
<td>800</td>
<td>18</td>
<td>3</td>
<td>8</td>
<td>180</td>
<td>114</td>
<td>Not Spherical</td>
<td>24.0</td>
</tr>
<tr>
<td>PEN7</td>
<td>3.0</td>
<td>800</td>
<td>18</td>
<td>3</td>
<td>8</td>
<td>184</td>
<td>100</td>
<td>Not Spherical</td>
<td>62.0</td>
</tr>
<tr>
<td>PEN6</td>
<td>5.0</td>
<td>800</td>
<td>18</td>
<td>3</td>
<td>8</td>
<td>184</td>
<td>115</td>
<td>Not Spherical</td>
<td>88.0</td>
</tr>
</tbody>
</table>

*Table 2.25 The Effect of Feed Concentration on Spray Drying of Pentamidine Isethionate.*
Plate 2.10 Photograph of the Atomised Spray as it Emerges from the Spray Dryer Atomiser.
2.4 Discussion

All the drug materials investigated spray dried successfully, resulting in a transformation in physical appearance from that of the starting material, except isoprenaline hydrochloride. It may be possible however, to improve the spray drying of isoprenaline hydrochloride with further manipulation of the spray drying parameters. Isoprenaline sulphate, salbutamol base and salbutamol sulphate could all be spray dried to produce powders with spherical particles in the respirable size range ($\leq 10 \mu m$). This is in keeping with previous work, where other drug materials have been shown to produce microfine spherical particles on spray drying, (Corrigan et al, 1984). The median particle size measured by laser diffraction was generally larger than from scanning electron microscopy. This is probably a consequence of the technique of measurement, the scanning electron microscope being one of direct visual measurement (projected area diameter) in contrast to the laser diffraction measurement, which is one of volume distribution. From the results it can be seen that the spray drying process is very dependent on the material used, this observation has been noted in earlier work in this area, (Marshall and Madison, 1955; Duffie and Marshall, 1953a). For example, pentamidine isethionate did not under the conditions investigated produce individual spherical particles. With manipulation of the spray drying parameters for example, with increase in aspirator level (the rate at which the air is pulled through the apparatus) and heat control and decrease in pump speed and feed concentration, the particles tended towards sphericity. All of these parameters would lead to greater evaporation of solvent at a given time. Further manipulation may yield the desired product characteristics. Certain general trends could be deduced from the results obtained:- As feed concentration was increased, the percentage yield and, in the case of isoprenaline sulphate and salbutamol sulphate, the particle size were increased. This would be expected as there would be a higher concentration of dissolved solid in each droplet. Because the particle size increases fewer fines are present to be carried out with the exhaust air and hence the higher yield. In the case of salbutamol base and salbutamol sulphate, yield was seen to increase with an increase in inlet temperature. Lower temperatures were however, required for spherical particles when spray drying salbutamol base, the higher temperatures caused
material degradation. Therefore, the inlet temperature used must be chosen carefully, it must be a balance between, running the dryer efficiently (the higher the inlet temperature the greater the thermal efficiency) and the product requirements. An increase in the rate at which the feed solution is pumped into the dryer increases the quantity of solvent being evaporated at any one time, this results in a lower surrounding air temperature and consequently as the pump rate is increased further, a point is reached where evaporation is insufficient, resulting in a wet product. Spray flow level increases, when drying isoprenaline sulphate, were seen to increase yields. Although particle size measurements were not recorded, in this case, previous work has indicated that an increase in air speed reduces the particle size of the droplet, (Castleman, 1931), and hence decreasing the final particle size. Differences in particle size and percentage yield observed between batches of spray dried material were small and probably not statistically significant. It should be noted that the yield measurements in this case were crude and with the lower yields especially, there is a degree of error. A more rationalised approach than changing one factor at a time is required for observations to be made within a sensible time frame.

A knowledge of drop size and size distribution from an atomiser is useful for performance prediction, (Kim and Marshall, 1971). Photography of the atomised spray proved to be difficult using the above technique. It has been reported that spray droplets of less than 120 μm are difficult to distinguish by photographic methods, (Duffie and Marshall, 1953a). Drop sizes from pneumatic nozzles are usually small and therefore evaporation effects are significant hence the representative sample must be collected or measured carefully. Other techniques of measurement such as; direct collection of the spray droplets in a mineral oil and subsequent calculation of size distribution from the mass, (Gretzinger and Marshall, 1961), spray drying of a liquid which on atomisation solidifies, such as paraffin wax, (Kim and Marshall, 1971) or collection of the spray in vaseline, (Kumar and Prasad, 1971), have all been previously used successfully and may be tried as alternatives to photography.
2.5 Conclusions

The scanning laser diffraction sizing technique adopted was as follows; a small (≤0.5 mg) quantity of the powder dispersed in approximately 10 ml of cyclohexane by sonicating for 30 seconds. This suspension is then dropped into the measuring cell and sized immediately.

Photography of the atomised spray proved to be difficult using the above technique. Other techniques been previously investigated may be more suitable in this case.

Manipulation of the spray drying parameters resulted in the transformation of isoprenaline sulphate, salbutamol base, salbutamol sulphate into powders with spherical shaped particles in the respirable size range. The best spray drying conditions for each drugs, within the limitations of these experiments are summarised in table 2.26. Because of the numerous factors involved during the spray drying process one a time changes in a factor were found to be unsatisfactory for two reasons; firstly to find the most suitable conditions for any one material is time consuming and secondly single changes in an individual factor do not indicate any interactions between factors that may be present. It has been noted that a change in a primary factor has repercussions on other factors, for example a change in feed concentration will also cause a change in feed rate, (Nonhabel and Moss, 1971).
### Table 2.26 The Most Suitable Spray Drying Conditions for Isoprenaline Sulphate, Salbutamol Base and Salbutamol Sulphate.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Isoprenaline Sulphate</th>
<th>Salbutamol Base</th>
<th>Salbutamol Sulphate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spray Flow Rate, NL/h</td>
<td>800</td>
<td>800</td>
<td>800</td>
</tr>
<tr>
<td>Aspirator Level</td>
<td>15</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Pump Rate, ml min⁻¹</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Heat control Level</td>
<td>7</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Inlet Temp. °C</td>
<td>158</td>
<td>130</td>
<td>160</td>
</tr>
<tr>
<td>Outlet Temp. °C</td>
<td>124</td>
<td>70</td>
<td>120</td>
</tr>
<tr>
<td>Concentration, %w/v</td>
<td>10</td>
<td>1</td>
<td>25</td>
</tr>
</tbody>
</table>
Chapter Three
Factorial Design Analysis
Factorial Design Analysis

3.1 Introduction

The results obtained from the spray drying of isoprenaline hydrochloride, isoprenaline sulphate, salbutamol base, salbutamol sulphate and pentamidine isethionate, given in section 2.3.3, indicated that varying a single factor per experiment gave insufficient data for rationalisation of the spray drying process. To optimise experimentally the spray drying process in terms of the particle size and percentage yield, all the factors have to be considered simultaneously. A factorial experimental design was chosen to investigate which factors when spray drying, the model compound, salbutamol sulphate affected the percentage yield and the particle size of the resultant powder. Salbutamol sulphate was seen to spray dry well under a variety of conditions and was therefore, chosen as model drug on which to perform further work.

Factorial designs are used in experiments involving several factors, where it is necessary to study the joint effect of the factors on the response (Fell and Newton, 1971a). Each factor is investigated in relation to the other factors, that is, all factors are said to be crossed. In each complete trial or replicate of the experiment all possible combinations of the levels of the factors are investigated and the effect, that is the change in response produced by a change in the level of the factors, is determined. Using factorial designs has several advantages:

(i) They are more efficient than experiments investigating each factor independently.

(ii) Interactions between factors are determined by this type of design.

(iii) A factorial design allows the effects of a factor to be estimated at several levels of other factors yielding conclusions that are valid over a range of experimental conditions.
3.2 Methods

A $2^4$ factorial design was chosen, that is four factors, involved in the spray drying process, were investigated at two levels, one high and one low, (table 3.1). The factors studied were; inlet temperature control, aspirator level, pump speed (rate at which solution is pumped into the dryer) and the concentration of salbutamol sulphate solution used. All experiments were carried out on a Büchi 190, mini spray dryer, using the method outlined in section 2.2.2 and the particle size of the powders produced were determined by laser diffraction (Malvern 2600C), suspended in cyclohexane (section 2.2.4). The yield of the product was determined by the method given in section 2.2.3.

The hypothesis tested is given below;
$H_0 = \text{a change in each factor is not significant ie. no difference between treatment means.}$

$H_1 = \text{there is a difference in treatment means.}$

<table>
<thead>
<tr>
<th>Notation</th>
<th>Factors</th>
<th>Levels investigated</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Pump Speed level</td>
<td>3 (5 ml min$^{-1}$), 5 (7 ml min$^{-1}$)</td>
</tr>
<tr>
<td>B</td>
<td>Aspirator level</td>
<td>10, 18</td>
</tr>
<tr>
<td>C</td>
<td>Heat control</td>
<td>8 (150 °C), 10 (180 °C)</td>
</tr>
<tr>
<td>D</td>
<td>Concentration of Salbutamol Sulphate</td>
<td>10% w/v, 20% w/v</td>
</tr>
</tbody>
</table>

*Table 3.1 Factors and the levels used in the Experimental Factorial Design.*
Chapter Three - Factorial Design Analysis

The levels for each factor were chosen as a result of previous experience with spray drying of salbutamol sulphate. Pump speeds at the bottom end of the range were chosen because high pump speeds produced very moist products since there was insufficient time for full evaporation of the solvent to take place. Heat control temperatures have to be high enough for the product to be dried but not so that chemical decomposition occurs. Very low concentrations lead to very fine particles which are carried out with the exhaust and very high concentrations, that is near saturation levels are difficult to obtain. Aspirator levels below 10 lead to moist products, therefore levels of 10 and 18 were chosen. Throughout all the experiments the spray flow rate was kept at constant rate of 800 NI h\(^{-1}\) (NI=normliter)

Notation

Each capital letter represents a factor. The subscript \(_0\) represents a factor at its lowest level, for example \(\text{C}_o\), represents a feed concentration of 10% w/v. Similarly the subscript \(_1\) represents the factor at its higher level. For each trial or replicate the combination of factors used is represented by a series of lower case letters. The high level of any factor is denoted by the corresponding lower case letter and the low level of a factor in the combination is denoted by the absence of the corresponding letter. For example the notation (ab), corresponds to the following combination; pump speed, 7 ml min\(^{-1}\); aspirator level, 18; heat control level, 8 and a feed concentration of 10% w/v. That is factors A and B are at their high levels and factors C and D are at the low level. When all the factors are at their lowest value the combination is represented by (1). The number of replicates is represented by \(n\) and the \(n\)th factor by \(k\).
3.3 Results and Statistical Analysis

3.3.1 Results

3.3.1.1 Particle Size Data

The results for the particle size analysis of the spray dried powers produced are given in table 3.2.

<table>
<thead>
<tr>
<th></th>
<th>A₀</th>
<th>A₁</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B₀</td>
<td>B₁</td>
</tr>
<tr>
<td>D₀</td>
<td>10.0</td>
<td>8.2</td>
</tr>
<tr>
<td></td>
<td>8.5</td>
<td>7.8</td>
</tr>
<tr>
<td></td>
<td>18.5=(1)</td>
<td>16.0=c</td>
</tr>
<tr>
<td>D₁</td>
<td>8.5</td>
<td>7.4</td>
</tr>
<tr>
<td></td>
<td>6.0</td>
<td>8.4</td>
</tr>
<tr>
<td></td>
<td>14.5=d</td>
<td>15.8=cd</td>
</tr>
</tbody>
</table>

Table 3.2 Particle Size Results for Experimental Factorial Design.

Where, the factors A represents the pump speed, B is the aspirator level, C the heat control and D is the salbutamol sulphate concentration. All particle size measurements are given in μm. The subscript ₀ means that the factor is at its lowest level and subscript ₁ indicates that the factor is at the high level, eg. C₁ represents a concentration of 20%).
### 3.3.1.2 Percentage Yield Data

The percentage yield for each batch of spray dried salbutamol sulphate is given in table 3.3.

<table>
<thead>
<tr>
<th></th>
<th>A₀</th>
<th>A₁</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B₀</td>
<td>B₁</td>
</tr>
<tr>
<td></td>
<td>C₀</td>
<td>C₁</td>
</tr>
<tr>
<td>D₀</td>
<td>47.96</td>
<td>28.00</td>
</tr>
<tr>
<td></td>
<td>56.00</td>
<td>38.00</td>
</tr>
<tr>
<td></td>
<td>103.96</td>
<td>66.00=a</td>
</tr>
<tr>
<td></td>
<td>=c</td>
<td>=b</td>
</tr>
<tr>
<td>D₁</td>
<td>62.00</td>
<td>57.00</td>
</tr>
<tr>
<td></td>
<td>57.00</td>
<td>40.00</td>
</tr>
<tr>
<td></td>
<td>119.00</td>
<td>97.00</td>
</tr>
<tr>
<td></td>
<td>=d</td>
<td>=cd</td>
</tr>
</tbody>
</table>

*Table 3.3 Percentage Yield Results for Experimental Factorial Design.*
3.3.2 Statistical analysis of $2^4$ Factorial Experimental Design.

(Montgomery, 1984).

There are several general assumptions made when using a factorial design, these are:

(i) All factors are fixed.

(ii) Designs are completely randomised.

(iii) The usual normality assumptions are satisfied.

With a $2^4$ factorial design it is assumed that the response is approximately linear over the range of the factor levels chosen. The statistical analysis can be broken down into five steps as follows:

(1) Calculation of the contrast for each source of variation.

To estimate an effect or compute the sum of squares associated with that effect it is necessary to first determine the contrast associated with that effect. The contrast for each effect can be determined by the following equation (eqn. 3.1)(for factor A...to k).

$$\text{Contrast}_{AB...A_k} = (a\pm 1)(b\pm 1)...(k\pm 1)$$

Equation 3.1

When using the above equation "1" is replaced by (1) in the final expression. The sign in each parenthesis is negative if the factor is included and positive if it is not.

Eg. using the data above;

$$\text{Contrast}_{AB} = (a-1)(b-1)(c+1)(d+1)$$

$$= (ab-a+1)(cd+d+c+1)$$

$$= abcd-bcd-acd+cd+abd-bd-ad+d+abc-bc-ac+c+ab-b-a+(1)$$

$$\text{Contrast}_{AB} = (15.8)-(16.5)-(16.2)+(15.8)+(17.7)-(22.3)-(16.6)+(14.5)+(11.9)-(11.8)-(14.8)+(16.0)+(13.9)-(13.5)-(17.1)+(18.5) = -4.7$$

The contrast constants for all variations can be calculated by this means, see table 3.4.
### Table 3.4 Contrast Constants for the 2^4 Factorial Design.

| A | B | A | B | C | A | B | C | A | B | D | A | B | D | A | B | C | A | B | C | D | A | B | C | D | A | B | C | D |
| (1) | - | - | + | - | + | + | - | - | + | + | - | + | - | - | + |
| a | + | - | - | - | - | + | + | - | - | + | + | + | - | - |
| b | - | + | - | - | + | - | + | - | + | - | + | + | - | - |
| ab | + | + | - | - | + | + | - | - | + | + | + | + | - | - |
| c | - | - | + | + | - | - | - | + | - | + | + | - | - | + | - |
| ac | + | - | - | + | + | + | - | - | + | + | - | - | + | - |
| bc | - | + | - | - | + | - | - | + | - | + | - | + | + | - |
| abc | + | + | + | + | + | + | + | - | - | - | - | - | - | - | - |
| d | - | - | + | - | + | + | - | - | + | - | + | + | - | - |
| ad | + | - | - | - | - | + | + | - | - | - | - | + | - | - |
| bd | - | + | - | - | + | - | + | - | - | + | - | - | + | - |
| abd | + | + | - | - | - | - | + | - | + | + | + | - | - | - |
| cd | - | - | + | + | - | - | + | - | + | - | - | + | - | - |
| acd | + | - | - | + | + | - | - | + | - | + | - | + | - | - |
| bcd | - | + | - | - | + | - | + | - | + | - | + | - | - | + |
| abcd | + | + | + | + | + | + | + | + | + | + | + | + | + | + |

Chapter Three - Factorial Design Analysis
Chapter Three - Factorial Design Analysis

(2) Calculation of sum of squares for each variation.

The general formulation for the sum of squares is given by equation 3.2:

\[ SS_{AB\cdot K} = \frac{1}{n}2^k \times (\text{contrast}_{AB\cdot K})^2 \]  
Equation 3.2

Eg. using the data from table 3.2,

\[ SS_{ab} = \frac{1}{2} \times 2^4 \times (-4.7)^2 \]
\[ = 0.6903 \]

The sum of squares for the total is calculated as follows (eqn. 3.3); 

\[ SS_T = \sum_{i=1}^{a} \sum_{j=1}^{b} \sum_{l=1}^{c} \sum_{d} y_{ijl}^2 - \frac{\sum_{i=1}^{a} \sum_{j=1}^{b} \sum_{l=1}^{c} \sum_{d} y_{ijl}^2}{2^k n} \]  
Equation 3.3

Eg. using data given in table 3.2,

\[ SS_T = 2102.05 - (252.9)^2 / 32 = 103.35 \]

The sum of squares of the error can be found by subtracting the individual sum of squares, for each variation, from the sum of squares of the total.

\[ SS_E = SS_T - (SS_A + SS_B + SS_{AB}) \]  
Equation 3.4

Eg. using the data given in table 3.2,

\[ SS_E = 103.35 - 49.50 = 53.86 \]
(3). Calculation of degrees of freedom.

Degrees of freedom, that is the number of independent values used in calculating the statistic minus the number of restrictions placed on the data, can be calculated, see table 3.5.

<table>
<thead>
<tr>
<th>Effect</th>
<th>Degrees of freedom</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>(a-1)</td>
</tr>
<tr>
<td>B</td>
<td>(b-1)</td>
</tr>
<tr>
<td>AB interaction</td>
<td>(a-1)(b-1)</td>
</tr>
<tr>
<td>ABC interaction</td>
<td>(a-1)(b-1)(c-1)</td>
</tr>
<tr>
<td>Error</td>
<td>ab...k(n-1) ie.2^k(n-1)</td>
</tr>
<tr>
<td>Total</td>
<td>2^n-1</td>
</tr>
</tbody>
</table>

*Table 3.5 Calculation of Degrees of Freedom in Factorial Design Analysis.*

(4). Calculation of mean square for each variation.

**Mean square = sum of squares / degrees of freedom** \[ \text{Equation 3.5} \]

\[
\text{Eg. } \quad \text{MS}_A = \frac{1/(n2^k)}{\text{contrast for A}} / (a-1)
\]

Using data from table 3.2,

\[
\text{MS}_A = 0.75/1
\]

\[= 0.75\]
(5). Calculation of $F_0$

$F_0$ is the ratio used to determine which effects are significant and is calculated as follows;

$$F_0 = \frac{\text{mean square of effect}}{\text{mean square of error}} \quad \text{Equation 3.6}$$

ie. $F_0 = \frac{\text{MS}_A}{\text{MS}_E}$

Using data in table 3.2 for a,

$$F_0 = \frac{0.75}{0.36} = 2.083$$

The five calculation steps above are known as analysis of variance. All the data given in table 3.2 was analysed see table 3.6 for the results.
Chapter Three - Factorial Design Analysis

Analysis of Variance

<table>
<thead>
<tr>
<th>Source of variation</th>
<th>Contrast</th>
<th>Sum of Squares</th>
<th>Degrees of Freedom</th>
<th>Mean Square</th>
<th>$F_0$</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>-4.9</td>
<td>0.75</td>
<td>1</td>
<td>0.75</td>
<td>0.22</td>
</tr>
<tr>
<td>B</td>
<td>-6.1</td>
<td>1.16</td>
<td>1</td>
<td>1.16</td>
<td>0.34</td>
</tr>
<tr>
<td>AB</td>
<td>-4.7</td>
<td>0.69</td>
<td>1</td>
<td>0.69</td>
<td>0.2</td>
</tr>
<tr>
<td>C</td>
<td>-15.3</td>
<td>7.32</td>
<td>1</td>
<td>7.32</td>
<td>2.17*</td>
</tr>
<tr>
<td>AC</td>
<td>+2.1</td>
<td>0.14</td>
<td>1</td>
<td>0.14</td>
<td>0.04</td>
</tr>
<tr>
<td>BC</td>
<td>-7.5</td>
<td>1.76</td>
<td>1</td>
<td>1.76</td>
<td>0.52</td>
</tr>
<tr>
<td>ABC</td>
<td>+5.1</td>
<td>0.81</td>
<td>1</td>
<td>0.81</td>
<td>0.24</td>
</tr>
<tr>
<td>D</td>
<td>+17.9</td>
<td>10.01</td>
<td>1</td>
<td>10.01</td>
<td>2.97*</td>
</tr>
<tr>
<td>AD</td>
<td>-0.7</td>
<td>0.02</td>
<td>1</td>
<td>0.02</td>
<td>5.9x10^{-3}</td>
</tr>
<tr>
<td>BD</td>
<td>+24.5</td>
<td>18.76</td>
<td>1</td>
<td>18.76</td>
<td>5.57**</td>
</tr>
<tr>
<td>ABD</td>
<td>-10.9</td>
<td>3.72</td>
<td>1</td>
<td>3.72</td>
<td>1.11</td>
</tr>
<tr>
<td>CD</td>
<td>+1.7</td>
<td>0.09</td>
<td>1</td>
<td>0.09</td>
<td>0.027</td>
</tr>
<tr>
<td>ACD</td>
<td>+2.3</td>
<td>0.16</td>
<td>1</td>
<td>0.16</td>
<td>0.049</td>
</tr>
<tr>
<td>BCD</td>
<td>-9.7</td>
<td>2.94</td>
<td>1</td>
<td>2.94</td>
<td>0.87</td>
</tr>
<tr>
<td>ABCD</td>
<td>+6.1</td>
<td>1.16</td>
<td>1</td>
<td>1.16</td>
<td>0.34</td>
</tr>
<tr>
<td>Error</td>
<td>-</td>
<td>53.86</td>
<td>16</td>
<td>3.37</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>-</td>
<td>103.35</td>
<td>31</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3.6 Results from the Analysis of Variance Using Particle Size Data.

* 75% confidence ie. $F_0$ is greater than or equal to 1.45
** 95% confidence ie. $F_0$ is greater than or equal to 4.49
Chapter Three - Factorial Design Analysis

The null hypothesis can be rejected that is, there is a difference in the treatment means. It can be seen from the results above that within the limitations of this experiment that no individual parameter is responsible for the particle size of spray dried salbutamol sulphate. The interaction between the concentration of the salbutamol sulphate and the aspirator however, has been shown to have a significant effect on particle size (95% confidence).

Similarly, using the same experimental conditions as above, the percentage yield data can be analyzed to show which factors influence the percentage yield when salbutamol sulphate is spray dried. The hypothesis tested in this case would be as follows:

\[ H_0 = \text{a change in each factor is not significant.} \]
\[ H_1 = \text{there is a difference in treatment means.} \]

Using the results given in table 3.3 the analysis of variance was calculated and the results are shown in table 3.7.

The null hypothesis can be rejected, that is there is a difference between the treatment means. It can be seen from the analysis of variance that, within the limitations of this experiment, factors B (95% confidence), D (97.5% confidence) and the interaction AC (95% confidence) influence percentage yield. That is the aspirator level, the concentration of salbutamol sulphate and the interaction between pump speed and concentration influence percentage yield of the product.
Chapter Three - Factorial Design Analysis

Analysis of Variance

<table>
<thead>
<tr>
<th>Source of variation</th>
<th>Contrast</th>
<th>Sum of Squares</th>
<th>Degrees of Freedom</th>
<th>Mean Square</th>
<th>( F_0 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>+69.25</td>
<td>149.86</td>
<td>1</td>
<td>149.86</td>
<td>1.59</td>
</tr>
<tr>
<td>B</td>
<td>+134.83</td>
<td>568.10</td>
<td>1</td>
<td>568.10</td>
<td>6.04**</td>
</tr>
<tr>
<td>AB</td>
<td>-15.184</td>
<td>7.20</td>
<td>1</td>
<td>7.20</td>
<td>0.08</td>
</tr>
<tr>
<td>C</td>
<td>-47.11</td>
<td>69.35</td>
<td>1</td>
<td>69.35</td>
<td>0.74</td>
</tr>
<tr>
<td>AC</td>
<td>+130.75</td>
<td>534.24</td>
<td>1</td>
<td>534.24</td>
<td>5.68**</td>
</tr>
<tr>
<td>BC</td>
<td>+25.17</td>
<td>19.80</td>
<td>1</td>
<td>19.80</td>
<td>0.21</td>
</tr>
<tr>
<td>ABC</td>
<td>-36.81</td>
<td>42.34</td>
<td>1</td>
<td>42.34</td>
<td>0.45</td>
</tr>
<tr>
<td>D</td>
<td>+158.83</td>
<td>788.34</td>
<td>1</td>
<td>788.34</td>
<td>8.38*</td>
</tr>
<tr>
<td>AD</td>
<td>+40.81</td>
<td>52.05</td>
<td>1</td>
<td>52.05</td>
<td>0.55</td>
</tr>
<tr>
<td>BD</td>
<td>-44.89</td>
<td>62.97</td>
<td>1</td>
<td>62.97</td>
<td>0.70</td>
</tr>
<tr>
<td>ABD</td>
<td>+21.25</td>
<td>14.11</td>
<td>1</td>
<td>14.11</td>
<td>0.15</td>
</tr>
<tr>
<td>CD</td>
<td>-58.83</td>
<td>108.16</td>
<td>1</td>
<td>108.16</td>
<td>1.15</td>
</tr>
<tr>
<td>ACD</td>
<td>-64.81</td>
<td>131.26</td>
<td>1</td>
<td>131.26</td>
<td>1.39</td>
</tr>
<tr>
<td>BCD</td>
<td>-3.11</td>
<td>0.302</td>
<td>1</td>
<td>0.302</td>
<td>0.003</td>
</tr>
<tr>
<td>ABCD</td>
<td>+54.75</td>
<td>93.67</td>
<td>1</td>
<td>93.67</td>
<td>1.00</td>
</tr>
<tr>
<td>Error</td>
<td>-</td>
<td>1505.98</td>
<td>16</td>
<td>94.12</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>-</td>
<td>4147.73</td>
<td>31</td>
<td>133.80</td>
<td></td>
</tr>
</tbody>
</table>

Table 3.7 Results from the Analysis of Variance, Using Percentage Yield Data.

* 97.5% confidence, \( F_0 \) is greater than or equal to 6.12.
** 95% confidence, \( F_0 \) is greater than or equal to 4.49.
3.4 Conclusions

Statistically the interaction between the aspirator and the feed concentration was seen to affect the median particle size of the spray dried salbutamol sulphate. Whilst neither an increase in feed concentration or aspirator level (the rate at which the air is pulled through the spray dryer) alone had an effect on the particle size. The two factors combined however, interacted to give a significant change in particle size, that is when both factors were at their highest level they produced an increase in particle size.

Percentage yield of spray dried salbutamol sulphate was shown to be effected by the aspirator level, the feed concentration and the interaction between the pump rate and the feed concentration. This means that increased aspirator level, feed concentration and the combination of the increased pump rate and feed concentration lead to significantly higher yields.

It should be noted that there are several limitations to the factorial design; results obtained are only true for the spray drying of salbutamol sulphate, for this particular spray dryer and nozzle type and may not necessarily be true for other materials. It is assumed throughout that all the factors are fixed, the design is completely random and that any response that occurs between two levels is linear.

This method however, does provide a useful technique for investigating, in a systematic manner, the spray drying of other materials.
Chapter Four

Physico-Chemical Analysis
Physico-Chemical Analysis

4.1 Introduction
An ideal drug powder, for use in dry powder inhalation formulation would be one where the drug is presented in the respirable size range, is not adhesive, cohesive or static, flows well in and out of the liberation device (without an inert carrier material) and is stable in most atmospheric conditions. In this study the physico-chemical properties of spray dried salbutamol sulphate have been investigated and compared with those of the micronised drug, to determine whether spray drying can be considered a suitable means of controlled particle size reduction. The physical properties investigated were; flowability, particle size, aerodynamic diameter, in vitro deposition, density, hollowness and shape of the particles. The chemical properties studied were infra red spectroscopy, differential scanning calorimetry, potency and crystallinity (X-ray diffraction).

4.1.1 In Vitro Deposition Measurements
Particle size and size distribution measurements can indicate likely deposition of an aerosol in the respiratory tract. The aerodynamic behaviour of a particle however, is not characterised simply by particle size measurements. Aerosol device assessments therefore, are made using in vitro models of the human lung, which include the twin impinger, the multi-stage liquid impinger and the cascade impactor. These attempt to account for both the physiology of the lung and the behaviour of the particles within the airstream (aerodynamic behaviour). The in vitro model used in routine assessment of aerosols is the twin impinger, apparatus A given in the British Pharmacopoeia (BP) (1988a) (fig. 4.1), because of its simplicity, speed, and reproducibility. It is a simple two stage inertial separation device, the first stage (stage I) collecting the coarse aerosol fraction, representing oropharyngeal deposition (having an effective cut off diameter of approximately 6.4 μm, Atkins, 1992) and the second stage (stage II) collecting the finer fraction, representing pulmonary deposition, at a flow rate of 60
L min\(^{-1}\) (Hallworth and Westmoreland, 1987). The effective cut off diameter is the
size at which 50\% of the particles of that size pass (Hallworth and Andrews, 1976).

Figure 4.1 Twin Impinger.

The aerosol device, to be tested, is placed in the mouth piece of the impinger and
actuated. The aerosol cloud is then caused to flow through the apparatus by means
of a vacuum pump set at a certain air flow rate (usually, 60 L min\(^{-1}\)). The deposits
are collected as washings from stages I and II and analysed, usually by high
performance liquid chromatography (HPLC) or by ultraviolet spectroscopy (UV). This
has the added advantage of only determining the drug content deposited and hence any
dust or excipient particles that may be present are not falsely measured. The twin
impinger is a simplification of the multi-stage liquid impinger device developed by
May (1966), for the sizing of bacterial particles from an aerosol. The multi-stage
liquid impinger consists of a one piece borosilicate glass body, containing three or
four stages, connected by circular tubes of successively decreasing diameter.
Operation is similar to that of the twin impinger. The twin impinger is recognised as
a pharmacopeial method for MDI assessment and the dimensions of the apparatus
and methods for operation are given in the 1988(a) British Pharmacopoeia.

The coarse oropharyngeal fraction collected (approximately 40% for a MDI
formulation, Hallworth and Westmoreland, 1987) corresponds well with mouth
washing experiments (Hallworth and Andrews, 1976). The second stage fraction
however, is higher than is actually seen in vivo (Phillips et al, 1990). This is possibly
a consequence of in vivo post throat extra thoracic deposition. The results from the
twin impinger are presented as the respirable percentage, which makes it an ideal
method for comparisons between different formulations and stability studies. The
dimensions however, may alter the percentage fraction collected and therefore the
dimensions of the apparatus should be specified, (Atkins, 1992). A second, less
frequently used, twin impinger is also described in the BP (1988a), (apparatus B).
This has the same effective cut off diameter but is constructed from metal and has
different physical dimensions.

Other more complex inertial separation models for in vitro deposition have been
designed for aerosol evaluation (Hallworth and Andrews, 1976). These all work on
the principle that the human respiratory tract is an efficient filtering device,
fractionating aerosol particles in terms of their aerodynamic diameter (Chapter One).
Multi-stage liquid impingers and cascade impactor devices mimic this. They have the
added advantage that the mass fraction collected at each stage is given directly in
terms of equivalent aerodynamic diameters, all apparatus being calibrated to give
effective cut off diameters. There are currently many designs available, the cascade
impactor used in this research was the Anderson 1 ACFM Non-Viable Ambient particle size sampler (Andersen Samplers Inc., Georgia, USA) (fig. 4.2) and therefore will be the impactor described, the principles however, are consistent for all impactors.

The cascade impactor was developed originally as a means of monitoring particulates in the workplace, for health reasons. It consists of a preseparator, eight aluminium stages and a backup filter. Each stage containing between 96 to 400 precision drilled circular, orifices concentrically arranged. The diameter of the holes successively decrease with descending stages (sizes range from 0.1004 to 0.01000") each stage contains a removable stainless steel collection plate which is slightly smaller than the stage so allowing unimpacted particles to flow through into the next stage. Air is also allowed to flow centrally though a hole in each collection plate (fig. 4.3). As the air is pulled through the impactor by a pump (28.7 L min⁻¹) particles are drawn towards the collection plates by the multiple air jets created by the holes in each stage. Deposition of a particle at any one stage is dependant on its aerodynamic dimensions.

Ranz and Wong, (1952) showed that the deposition of a particle caused by an obstacle in its path is dependant on its inertial impaction parameter (eqn. 4.1)

\[ K = \frac{C\rho UD_p^2}{18\mu D_c} \]  

Equation 4.1

Where \( U = \)relative velocity, \( \rho = \)particle density, \( D_p = \)particle diameter, \( \mu = \)gas viscosity, \( D_c = \)diameter of round jet and \( C = \)Cunningham slip correction factor (which is \( C = 1+(0.16 \times 10^4/D_p) \), for normal temperature and pressure).

It should be noted that the same equation could be used to predict inertial impaction in the respiratory tract, \( D_c \) becoming the diameter of the airway. The Cunningham slip correction factor allows correction for small particles. As the particle diameter
approaches the mean free length of the gas molecules it tends to "slip" between the gas molecules more easily and hence across the bulk flow.

Figure 4.2 Anderson Mark II Cascade Impactor.
The inertial impaction efficiency is therefore slightly greater than would be predicted for particle diameters of one or two micrometers.

The air flow rate and the pressure drop through the impactor remains constant. The particle size collected at each stage is dependent on the orifice velocity of the stage, the distance between orifices and the collection surface and the deposition characteristics of the preceding stage (Andersen Samplers Inc., 1985). The combination of constant air flow and successive reduction in orifice size causes an increase in velocity of the air, this in turn causes impaction of the smaller particles. Any particles too small to be collected by the last stage are collected by the backup filter. The sample collected at each stage can then be directly represented by a size range, the effective cut off diameter representing the smallest particle that may be collected at that stage. Although there is some overlap in size between stages this is minimised by the use of circular orifices which give sharper cut off diameters, than rectangular orifices.
The cascade impactor has the advantage that the results obtained give a size distribution and consequently MMAD can be determined. The twin impinger was shown to be better at indicating differences between formulations, this is probably due to the greater operational flow rate, (Phillips et al, 1990). However distinction between formulations of similar aerodynamic diameter may be improved by representing the data as respirable dose rather than respirable fraction (Phillips et al, 1990). In general the cascade impactor gives more detailed, reproducible information than the twin impinger but is only suitable for dilute aerosols, impingers are not as sensitive to overloading, (Bell et al, 1973). Impactors have the potential problems of particles blowing off the collection plates and bouncing from the deposited stage to a lower one (Sem, 1984), however, this may be overcome by coating the collection plate surface with a sticky substance such as paraffin. Testing of MDIs or nebulisers is problematic as a result of solvent evaporation, this may be overcome be real time analysis of the suspended aerosol (Sem, 1984). This problem is not applicable to dry powder devices and therefore is not discussed fully here.

Other in vitro methods for aerosol evaluation include alternative aerodynamic diameter measuring instruments such as laser diffraction, described by Sem, (1984); the model lung developed by Kirk (1972), which was later modified by Davies et al (1976); mathematical modelling, using a series of algebraic equations based on experimental data, (Gonda, 1981b); microscopy; high speed flash photography; photomicrography and laser holography (Kirk, 1972).

4.1.2 Powder Flow
The flowability of a powder to be used in a dry powder inhaler (DPI) is especially important, for both the filling (Danish and Parrott, 1971) and the emptying of the device, to ensure reproducible dosaging. Ideally the flow should be such that the drug alone could be used in the device without the need for a carrier material, which presents added formulation problems; such as the degree of adherence between the two materials.
Chapter Four - Physico-Chemical Analysis

The flowability of a powder may be described as free flowing, non-free-flowing or as exhibiting floodable flow (Carr, 1965a): A free flowing powder is one which flows steadily and consistently, as individual particles, even through a fine orifice. A non-free flowing powder will tend to flow not as individual particles but in clumps or as whole mass. Floodable flow can be described as an unstable flow that is analogous to liquid flow. It can be gushing, spattering, uncontrollable or discontinuous.

4.1.2.1 Properties Affecting Powder Flow

Particulate properties: size, shape, crystallinity, hardness, hygroscopicity and bulk powder properties: density (aerated and tapped), size and shape distribution, surface energy, inter-particle cohesion, adhesion to surfaces (Brown, 1961) and specific surface area are all known to affect powder flow.

Particle Size and Size Distribution

The size of a particle is usually represented by the diameter of an equivalent sphere dependant on the method of measurement selected. A decrease in particle size has been shown to increase flow up to a maximum, after which further size reduction causes a decrease (Danish and Parrott, 1971). The presence of small particles, those less than 10 μm, promotes cohesiveness of the powder. This is thought to be a consequence of Van Der Waals forces acting upon the particles. The calculated Van Der Waals force for a particle of diameter less than 10 μm is greater than the force of gravity acting upon it, therefore particles of this size are cohesive. For larger particles the gravitational force, which increases with the cube of the diameter, becomes dominant. The actual attraction however, may be smaller because a close approach cannot be achieved, (Neumann, 1967). A material containing larger particles is therefore, not cohesive unless other attractive forces, such as electrostatic charges and forces between absorbed films come into play (Brown, 1961).
Chapter Four - Physico-Chemical Analysis

The size distribution measured depends very much on the method of analysis. Whatever method is used, it gives an indication of the degree of heterogeneity and evenness of spread within the powder. Addition of a small quantity of fines to a mix has been noted to improve flow (Danish and Parrott, 1971). Heterogeneous powders however, have the added complication of segregation of particles according to size during flow. Size distribution affects other parameters such as density which in turn affects flow. The wider the size distribution the greater the potential for a higher packing density, the smaller particles filling the voids between the larger ones and hence the greater the mass per unit volume (Danish and Parrott, 1971).

Particle Shape

Anisometric particles, those that are elongated or flat, tend to align their axes with the direction of flow. When this orientation is achieved, flowability is improved, there being less internal friction than with isometric particles. The flow of anisometric particles is difficult to characterise and only if the correct orientation is found will the flow be improved. Carr, (1965a) noted that more or less spherical shaped, smooth, uniform particles favoured free flow.

The particle shape also affects powder bulk density; anisometric particles tend to give more open packings of high porosity, which can be more easily deformed than packings containing isometric particles.

Surface Texture and Surface Free Energy

A high degree of visually observable surface porosity and roughness is connected with a predominance of frictional and cohesive effects and poor flowability. There are differences between the structure of the surface and the body of the powder, which may be detected by the chemical behaviour and affect the physical behaviour of the powder. Differences such as polarization of surface ions and adsorption of foreign molecules may occur as compensatory mechanisms for the energy derived from broken atomic bonds and other physico-chemical sources in order to reduce the
surface free energy and as a consequence effect cohesiveness between particles. In general the lower the surface energy the more free flowing the powder will be (Carr, 1965a). Surface free energy is discussed more fully in Chapter 5.

Crystallinity and Density
The crystallinity of a particle is determined by its chemical structure and affects the true density, deformation strength and the electrical properties. The more crystalline the powder the greater the tensile strength and the better the flow (Carr, 1965a). The density of the particle affects the rheological properties of the powder by its influence on the relative contributions of gravity and surface forces. High particle density favours free flow (Carr, 1965a).

Specific Surface Area
Surface area is related to size and structure of the particles. The larger the specific surface area the harder it is for particles to roll over each other and hence there is deterioration in flow.

Hygroscopicity
The degree of moisture within a powder will affect its interparticulate reactions and handling properties (Eaves and Jones, 1970). Increased moisture content has been reported to increase angle of repose for a number of powders (Craik and Miller, 1958). At low levels of humidity, interaction is largely governed by electrostatic forces, at high humidities however, the capillary force due to water vapour condensation at the particle interface becomes more important. Dissipation of surface electrostatic charge with increase in humidity has been noted and is thought to be caused by adsorbed moisture on the surface causing an increase in electrical conductivity between the surface and surrounding atmosphere. The critical relative humidity required to dissipate surface electrostatic charge is dependent on the material and type of adsorption. In general an increase in relative humidity is accompanied by
an increase in adhesion. The capillary force generated is affected by particle size, the larger the particle the greater the force (Kulvanich and Stewart, 1988).

There are four types of force that are important for the adhesion of a particle to a surface; molecular, electrical, capillary and interfacial. Molecular forces remain constant at any humidity. Electrostatic forces, include electrical double layer formation at contact points, which occur up to the point where charge leakage occurs, and coulombic interaction of electrical charge distributed over the particle surface due to previous electrifications, which cause increased adhesion, depending on the degree of static electrification and treatment of the material, at low to intermediate humidities. Capillary forces are the major cause of adhesion at high humidities. The relative humidity during processing and the moisture content of a powder has been noted to affect its adhesiveness and hence blending and storage due to the changes in forces acting upon it (Kulvanich and Stewart, 1988). The presence of moisture can influence the mechanical strength of a powder. The tensile strength of a powder has been reported to increase to a maximum with increase in moisture content. This was thought to be a consequence of reduced interparticulate separation caused by an increase in Van Der Waals forces and the formation of pendular bridging. The increase in tensile strength was seen to be affected by particle size, the smaller the particle size the more susceptible the powder (Eaves and Jones, 1972). However, it is only the surface adsorption the affects the tensile and shear properties of the powder. For example the tensile and shear properties of sodium cromoglycate at different humidities remained virtually constant although the material is very hygroscopic, because moisture is absorbed internally forming H-bonds (Chan and Pilpel, 1983).

4.1.2.2 Measurement of Powder Flow

Because powder flow is dependent on so many variables direct measurement is difficult. No universal method for measurement has been developed (Garrett, 1985). Powder flow is therefore evaluated by indirect measurements including angle of
repose, angle of spatula, compressibility, cohesiveness or uniformity, (all of which are described below) (Carr, 1965a, 1965b) flow through an orifice, (Danish and Parrott, 1971) and shear cell methods (York, 1980). No single method however takes into account all the factors affecting flow therefore measurements should be used in conjunction with each other (Garrett, 1985).

The Angle of Repose

The angle of repose is the constant angle between the horizontal and the slope of a cone-shaped powder heap. When a powder is placed in a heap the only force acting upon it is that of gravity. When in equilibrium, the forces of friction and interparticulate forces are equal to the gravitational force. For any one powder the angle of the cone cannot exceed a certain angle to the horizontal (angle of repose). Any particle that lies outside the angle will simply slide down the slope under the force of gravity (Neumann, 1967). The exact value obtained for the angle of repose depends on the method of measurement (Brown, 1961; Neumann, 1967; Train, 1955), whether it is the poured, tilted or drained angle. The angle of repose is dependent on the shape, (particles that depart from sphericity increase the angle) (Brown, 1961), size (although size has only a limited effect, monosized particles favour smaller angles), porosity, cohesion, fluidity, surface area, bulk of the powder (Carr, 1965a) and relative humidity (Neumann, 1967). The surface properties have been noted to have a greater influence on the angle than size effects (Neumann, 1967) and are considered to be an indication of interparticulate friction or resistance to movement within the powder (Brown, 1961). Whatever the measurement method, it is generally considered that angles below 40° are indicative of free flowing powders, whereas those powders with angles exceeding 50° are considered to be cohesive perhaps forming aggregates (Brown, 1961). The theoretical minimum for uniform spheres calculated from geometry is about 20° (Neumann, 1967). Angle of repose measurements are simple to preform and are used regularly for comparative investigations. There are however several criticisms of its use, these being that correlation between different methods of angle measurement is poor (Train, 1958), the test is not very sensitive for distinguishing between two materials of slightly different flow, the accuracy being
Chapter Four - Physico-Chemical Analysis

± 1° (Garrett, 1985) and there is sometimes difficulty in making measurements since
the cones produced are seldom symmetrical (Craik and Miller, 1958; Neumann, 1967).
The angle of repose measurement is useful however when used in conjunction with
other indirect flow measurements (Carr, 1965a).

Angle of Spatula
This is a very simple test where by a spatula of known dimensions is inserted
horizontally into the powder mass and then lifted straight out (still holding the spatula
horizontally). The angle formed by the powder on the spatula will depend on the
flowability of the material. A free flowing material will form one single angle of
rupture or internal friction (according to size of the particles) and a non-free flowing
material will form several irregular angles. The average of several measurements to
the horizontal is taken, the spatula is then tapped gently and the average recalculated.
The average of the two measurements gives the angle of spatula. The angle of
spatula, similar to the angle of repose, is an indirect measurement of cohesion, surface
area, size, shape, uniformity, fluidity, porosity and deformability. Generally the angle
of spatula is higher than the angle of repose for the same material, the exception being
only for very free flowing materials. Angles of less than 40° are indicative of free
flowing powders. The higher the angle of spatula the lower the flowability of the
sample (Carr, 1965a).

Compressibility (Density Measurements)
This really a measurement concerned with the density aspects of the powder. Carr,
(1965a) developed a compressibility ratio eqn. 4.2.

\[
\% \text{ Compressibility} = \left( \frac{P-A}{P} \right) \times 100
\]

Equation 4.2

Where A=aerated density (the weight per unit volume of a powder, g cm⁻³) and
P=packed density (the apparent density of a powder obtained when the receptacle is
tapped or vibrated under specific conditions).
Aerated bulk density is dependent on particle density, size, size distribution, shape, shape distribution, specific surface area and porosity (Hausner, 1967). Packed bulk density is reliant on all the above properties and also on the interparticulate cohesive and frictional forces. Bulk density alone is not a useful means for evaluating flow, there being no direct relationship between the two (Carr, 1965a). However, when the aerated and packed bulk densities are expressed as a ratio, the information acquired is a good indication of the flow of a material. The more compressible the material the less flowable it will be. It is an indirect measurement of uniformity of size and shape, deformability, surface area, cohesion and moisture content (Carr, 1965a). Another ratio connecting aerated and packed densities is that of the Hausner ratio (P/A) (Hausner, 1967). An alternative method for studying the apparent density distributions of spray dried powders has been described. Where the powders are suspended in a series of fluids of varying densities (Verhey and Lammers, 1973). The disadvantage of this method however is that the samples are destroyed and that measurement is tedious.

The rate at which the packed density is achieved is another useful indication of how a material will behave. The rate of packing is dependent on the size and shape of the particles and their distribution within the powder mass and the presence of arches and bridges between the particles (Carr, 1965b). For example, a monosized powder with near symmetrical particles will quickly find its best arrangement, the more heterogeneous the sample becomes the greater the packing rate will be. In general the higher the rate of packing down and the smaller the difference between the aerated and packed bulk density the better the flowability of the material (Neumann, 1967).

**Cohesiveness or Uniformity**

Cohesiveness is especially important for powders of small particle size, uniformity index is used more for granular or powder granular materials. Cohesiveness in terms of flow is the measure of the forces of cohesion existing on the surface of the particles. There are no apparent cohesive forces on the surface of dry granular powders that can be measured, unless enough force is used to press them together.
Chapter Four - Physico-Chemical Analysis

(Carr, 1965a). Many indirect methods indicating the cohesive forces between particles exist, these being; tests of mobility, sieve analysis, including rate of sieving, angular characteristics, split plate methods and shear cell techniques. These have all been reviewed in an article by Jones (1968), where it was noted that the most useful method was that of the shear cell developed by Jenike. In this research however, the method used to measure cohesiveness was described by Carr (1965a). This technique uses the retention of material on a nest of sieves, vibrated for a set time depending on the materials working bulk density (eqn. 4.3)

\[ W = (P - A) C + A \quad \text{Equation 4.3} \]

Where W, P and A are the working, packed and aerated bulk densities respectively and C is Carr’s compressibility ratio (eqn. 4.2).

The test is a direct determination of the force required to pull the material aggregates apart. A uniformity coefficient can be determined (Carr, 1965a), which is a value determined by dividing the width of sieve opening that will pass 60% of the material by the width of the sieve opening that will pass 10% of the sample. This coefficient is an indirect measure of size, shape and compressibility. The more uniform the material in size and shape the more flowable it is likely to be.

Other Methods for Flow Determination include flow through an orifice but this technique is only suitable for mildly to non cohesive materials and therefore was not used in this case. Shear cell methods (Jones, 1968), are more complicated and time consuming but are extremely useful for the prediction of flow through hoppers.
4.2 Materials and Methods

4.2.1 Materials

Salbutamol Sulphate, Micronised.
Micro Macinazone SA, Microgrinding Ltd., Switzerland.

Lactose, Medium Grade.
Batch No. 2325, Lactochem, Slatney, Cheshire, UK

Lactose Intermediate Grade.
Batch no. A36791, Lactochem, Slatney, Cheshire, UK.

Cyclohexane HPLC Grade.
Aldrich Chemicals Co. Inc., USA.

Avicel PH101 (Microcrystalline cellulose and sodium carboxy methylcellulose)
FMC Corporation, Philadelphia, USA.

Aerosil 200 (Colloidal silicone dioxide)
Degussa, Pigments Division, Frankfurt, W. Germany.

4.2.2 Spray Drying

A Büchi 190 mini spray dryer (section 2.2.2) was used to spray dry a solution of salbutamol sulphate. A 10% solution of salbutamol sulphate was spray dried under the following conditions; pump rate, 5 (7 ml min⁻¹); air flow rate, 800 NI h⁻¹; aspirator level, 18; Inlet temperature, 151-153°C and outlet temperature, 80-85°C. These settings were chosen taking into consideration the data produced from preliminary
4.2.3 Particle Size, Size Distribution and Shape

Particles were viewed using the Phillips XL20, scanning electron microscope (S.E.M.), (section 2.2.4). S.E.M. has proved to be a particularly useful method for powder surface evaluation (Brittian et al, 1991) and has been used previously for observation of spray dried milk products (Buma and Henstra, 1971). Powders for S.E.M. were mounted onto an aluminum stub using double sided sticky tape, gold coated for 2-4 minutes at 40 mA, using a sputter coater (section 2.2.4). Samples were then viewed at accelerating voltages between 10-15 KV. Photographs were taken of these samples and were used for image analysis.

Size distribution was measured using laser diffraction (Malvern Lasersizer 2600c), by suspending the powder samples in cyclohexane, using the method described in section 2.2.4. Computer image analysis (Seescan, TPL6v00) was used to determine the size distribution of the spray dried material from the S.E.M. negatives, and for shape analysis of both the spray dried and micronised salbutamol sulphate. A video camera was used to obtain an electronic image from a S.E.M. negative through a microscope, which was then digitised. Digitisation is accomplished by the spiting of the image into a grid of rectangular picture elements (pixels). Each pixel is assigned a level of greyness according to the average intensity of the image. Image preparation is very important if this procedure is to be done effectively. The image must be of high contrast and external lighting kept to a minimum. This was achieved by using the negative, rather than a photograph of the particles, placed on an illuminated light box with the microscope positioned horizontally above and surrounded by black card, so eliminating external light effects. Once digitised, the image was manipulated to show regions of interest only and to eliminate background particles (thresholding), the computer then mapped out what it considered to be individual particles on which to perform the analysis. For each particle the Feret’s diameter (the perpendicular length between two tangents to the periphery of the particle’s width) was measured,
cumulative results from several negatives were taken (so that at least 400 particles 
were measured) to give a size distribution.

The shape analysis was performed on individual particles of both spray dried and 
micronised salbutamol sulphate. The image analyser examines shape by measuring the 
distance from the centre of mass of the particle to its perimeter, through 360°. The 
degree of scatter from the mean, is represented graphically as a scatter plot and 
expressed as a relative percentage standard deviation, which is the percentage 
deviation from the measured mean distance between the centre of mass and the 
perimeter. The closer scatter plot is to a straight line the more spherical the particle. 
A relative standard deviation of less than 5% indicates a spherical particle.

4.2.4 Specific Surface Area
This was measured by the Malvern Lasersizer during size distribution measurements 
and is derived from the volume measurements made by the Malvern.

4.2.5 Density Measurement
The apparent density of both the micronised and the spray dried salbutamol sulphate 
was calculated using eqn. 4.4.

\[
\text{Density} = \frac{\text{Mass}}{\text{Volume}} \quad \text{Equation 4.4}
\]

The true volume of the powders were measured using the Beckman, Model 930, Air 
Comparison Pycnometer (fig. 4.4).
4.2.6 Hollowness of Spray Dried Particles

Several techniques were employed to determine whether the particles of spray dried salbutamol sulphate were solid or hollow:

i) **Crushing;** A small amount of powder was sandwiched between two glass microscope slides and crushed. The resultant sample was then viewed using the S.E.M.

ii) **Grinding;** A small quantity of powder was ground using a mini pestle and motor and the resultant powder viewed using the S.E.M.

iii) **Embedding in an adhesive;** A small quantity of the powder was mixed with the adhesive Araldite® (epoxy resin adhesive), allowed to harden and snapped into pieces in the hope that some particles would be fractured. The pieces were then viewed under the S.E.M.
iv) **Freeze and fracture**: The material was frozen in a degassed liquid nitrogen slush (-180°C) at a rapid cooling rate (to reduce ice crystal formation). The frozen material was the crushed and viewed using a S.E.M. cryo system.

v) **Transmission electron microscopy (T.E.M.)**; By using transmission microscopy it was hoped that a high optical contrast could be produced to show areas of hollowness. Two methods were investigated, (a) Powder was placed on a support film and viewed using a Phillips 201C T.E.M. at an accelerating voltage of 100 kV. (b) Powder was dispersed on to a 1% colloidion coated 3.05 mm copper grids. Viewed under the Phillips CM20 T.E.M., at an accelerating voltage of 200 kV, without an objective aperture to avoid diffraction, on bright, normal and dark fields. This was performed at Cranfield College of Aeronautics.

vi) **Freeze fracture**: A little of the powder was dispersed in cyclohexane, frozen using a degassed liquid nitrogen slush and fractured using the hinge method for positive and negative imaging (Reichert freeze fracture system). Specimen surfaces were shadowed using carbon and platinum, removed from the vacuum, the powder dissolved and the replicas viewed using T.E.M. (Phillips 201C T.E.M.). The freeze fracture replicates were prepared at St. Mary’s Hospital, London.

### 4.2.7 X-Ray Diffraction

X-Ray diffraction was performed on both spray dried and micronised samples of salbutamol, using an X-ray generator PW1830, with a PW1820 diffractometer and PW1710 control system (Phillips, Cambridge, UK). The X-ray diffraction was performed courtesy of Sheffield Hallam University, Materials Research Institute, Department of Materials Science.

### 4.2.8 Differential Scanning Calorimetry (DSC)

DSC was carried out on both micronised and spray dried powders using the Perkin Elmer 7 Series Thermal Analysis System (Perkin Elmer Corporation, Germany).
Chapter Four - Physico-Chemical Analysis

Samples of around 7 mg were run at a rate of 10°C min⁻¹ over a temperature range of 40 - 400°C.

4.2.9 Potency

The potency of the spray dried material was compared to that of the micronised material, using a fluorometric method (Amico-Bowman Spectrofluorimeter, Serial No. U-54960-1, American Instruments Company, Maryland, USA). The excitation wavelength used was 224 nm and the emission 316 nm.

4.2.10 Infra-red Spectroscopy

Infra-red spectroscopy (IR) was performed using Perkin Elmer 841 Infrared spectrophotometer (Perkin Elmer Corporation, Germany), simply as a means of ensuring that salbutamol sulphate was not chemically altered by spray drying. Powder samples were scanned over the wavelength 800-3600 nm using KBr discs. IR spectra of micronised and spray dried salbutamol sulphate were compared to the BP (1988b) standard spectrum.

4.2.11 Powder Flow Measurements

As described in section 4.1.2.2, no one parameter can take into account all the factors responsible for the flow of a material, therefore, a series of measurements indicative of flow must be combined. Carr (1965a), developed a method whereby a series of tests namely, angle of repose, angle of spatula, compressibility, cohesiveness or uniformity (the choice of which depends on the coarseness of the powder), are measured and assigned an index number, depending on the measured value. The index values used were derived using different grades of sand as standards. The summation of these index values gave a measure of flowability. The flowability measurements made in this research are based on this method. In order to standardise
measurements and eliminate operator error, flow evaluation was made using the Hosokawa, Powder Characteristic Tester (Hosokawa Micrometrics Laboratory, Japan) (fig. 4.5). The advantage of using this tester lies in the fact the all the dimensions and methods remain constant and results are reproducible.

The angle of repose was measured by coarse sieving the material by vibration into a funnel placed at a set height above a circular platform (fig. 4.6). Powder was allowed to flow onto the platform until it was seen to overflow. The angle of the cone formed was then measured, from both sides and the average taken as the angle of repose.

Figure 4.5 Hosokawa, Powder Characteristic Tester.
Aerated and packed density were measured by causing the powder to flow through a coarse screen into a cylindrical vessel. The vessel was filled until overflowing and the excess scrapped off. The weight of the vessel was then recorded, an extension placed on the top, filled with extra powder and the whole device placed in an automatic tapping device. The rheostat was set to 216 seconds (50 tap cycle) and on completion the vessel levelled and reweighed. From the packed (P) and aerated (A) bulk density the compressibility ratio (C) was calculated from equation 4.5

\[ C = 100 \frac{(P+A)}{P} \]

Equation 4.5

Cohesion was measured using a nest of sieves (200, 100 and 60 mesh). Two grams of material were placed on the top mesh and the nest vibrated at an amplitude of 1 mm for a set time (T), calculated using equations 4.6 and 4.7.

\[ T = 20 + \frac{1.6 - W}{0.016} \]

Equation 4.6

\[ W = \frac{(P+A)C}{100+A} \]

Equation 4.7
Where P and A are the packed and aerated bulk density respectively, C is the compressibility, W is the dynamic bulk density.

After vibration the remaining powder on each sieve was weighed and the cohesion calculated using equations 4.8, 4.9 and 4.10:

\[
\frac{\text{Material on upper Sieve}}{2g} \times 100 \quad \text{Equation 4.8}
\]

\[
\frac{\text{Material on Centre Sieve}}{2g} \times 100 \times \frac{3}{5} \quad \text{Equation 4.9}
\]

\[
\frac{\text{Material on Bottom Sieve}}{2g} \times 100 \times \frac{1}{5} \quad \text{Equation 4.10}
\]

The summation of equations 4.8, 4.9 and 4.10 provides the value for cohesiveness.

(It should be noted that the measurement of cohesiveness will be affected if the particles have a tendency to be attracted to each other by electrostatic forces or form balls of material on vibration.)

The angle of spatula was measured using the apparatus shown in figure 4.7. The pan was placed in the powder tester holder and moved up until it touched the spatula. It was then filled with powder and lowered to leave angled material on the spatula. Three angle measurements were taken on each side of the heap and averaged. A weight on a slide next to the apparatus was raised along the slide and allowed to drop, so causing the powder to realign. The measurements were taken and the average recalculated. The average of these two averages was the figure used to describe the angle of spatula.
The uniformity index indicates the range of size distribution and can be obtained by sieving the powder, under investigation, on a nest of sieves and results computated using equation 4.11.

\[
\text{Uniformity Index} = \frac{\text{Aperture size through which 60\% of the powder passes}}{\text{Aperture size through which 10\% of the powder passes}}
\]

Equation 4.11

In this case the 60\% and 10\% values were obtained from powder size distributions measured using the Malvern Lasersizer with a powder feed adapter.

A measurement for flowability was achieved by using the data obtained from the above experiments and the index conversion chart shown in table 4.1. (Duplicate measurements were made for each sample).

Spray dried and micronised materials were seen to be very cohesive making direct flow measurements very difficult; although these were performed, an indirect method was also employed. Micronised and spray dried materials were added to Avicel and intermediate grade lactose in different concentrations and the flow of the mixtures evaluated. This was performed as a test of the flow promotion properties of the
Chapter Four - Physico-Chemical Analysis

materials. To test the suitability of this method, Avicel/Aerosil mixtures, using Aerosil concentrations of between 0-1%, were first used as a model. Powders were sieved before mixing, mixed for 10 minutes using the Turbula mixer (type T2C, Willy A. Bachofen AG, Machinen Fabrik Utengasse 15/17), run at a speed of 90 r.p.m, coarse sieved again (250 μm sieve) and mixed for a further 20 minutes.
<table>
<thead>
<tr>
<th>Degree of Flowability</th>
<th>Flowability Index</th>
<th>Necessity of Bridge-breaking measures</th>
<th>Angle of Repose</th>
<th>Compresibility</th>
<th>Angle of Spatula</th>
<th>Uniformity*</th>
<th>Cohesion**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Degree</td>
<td>Index</td>
<td>%</td>
<td>Index</td>
<td>Degree</td>
</tr>
<tr>
<td>Very Good</td>
<td>90 – 100</td>
<td>Not required</td>
<td>&lt;25</td>
<td>25</td>
<td>26 – 29</td>
<td>22.5</td>
<td>&lt;25</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>30</td>
<td>25</td>
<td>6 – 9</td>
<td>10</td>
<td>25</td>
</tr>
<tr>
<td>Fairly Good</td>
<td>80 – 89</td>
<td>Not required</td>
<td>31</td>
<td>22</td>
<td>32 – 34</td>
<td>22</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>35</td>
<td>21</td>
<td>12 – 14</td>
<td>15</td>
<td>33</td>
</tr>
<tr>
<td>Good</td>
<td>70 – 79</td>
<td>Sometimes Vibrator is required</td>
<td>35</td>
<td>19</td>
<td>37 – 39</td>
<td>18</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>40</td>
<td>17.5</td>
<td>17 – 19</td>
<td>20</td>
<td>40</td>
</tr>
<tr>
<td>Normal</td>
<td>60 – 69</td>
<td>Bridging will take place at the mar­</td>
<td>41</td>
<td>17</td>
<td>42 – 44</td>
<td>16</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ginal point</td>
<td>45</td>
<td>15</td>
<td>22 – 24</td>
<td>15</td>
<td>47</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>40</td>
<td>17</td>
<td>25 – 30</td>
<td>12</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>55</td>
<td>10</td>
<td>27 – 30</td>
<td>10</td>
<td>62</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10</td>
<td>62</td>
<td>10</td>
<td>22</td>
<td>10</td>
</tr>
<tr>
<td>Bad</td>
<td>20 – 39</td>
<td>Powerful measures should be provided</td>
<td>56</td>
<td>7.5</td>
<td>57 – 64</td>
<td>5</td>
<td>76</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>65</td>
<td>5</td>
<td>33 – 36</td>
<td>10</td>
<td>77</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>90</td>
<td>5</td>
<td>37 – 36</td>
<td>5</td>
<td>78</td>
</tr>
<tr>
<td>Very Bad</td>
<td>0 – 19</td>
<td>Special apparatus and techniques are</td>
<td>66</td>
<td>9.5</td>
<td>67 – 89</td>
<td>5</td>
<td>91</td>
</tr>
<tr>
<td></td>
<td></td>
<td>required</td>
<td>90</td>
<td>0</td>
<td>39 – 45</td>
<td>0</td>
<td>92</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0</td>
<td>&gt;45</td>
<td>0</td>
<td>&gt;99</td>
<td>0</td>
</tr>
</tbody>
</table>

* Use these figures for granules or granular powder with which the uniformity can be measured.

** Apply these figures for fine and cohesive powders with which the cohesion can be measured.

Table 4.1 Flowability Index Values
(Reproduced from the Hosowaka manual)
4.2.12 In Vitro Deposition

The aerodynamic behaviour of spray dried and micronised salbutamol sulphate was investigated using the drug alone and also in the presence of a carrier material, lactose.

Powder was filled manually in hard gelatine capsules size 3, the weight of powder used in each case was between 500-600 mg, accurately weighed using a digital balance (Sartorius Ltd., Longmead Business Centre, Surrey, UK). Capsules were then loaded in a dry powder inhaler, the Rotahaler® (Glaxo, fig. 1.5) and liberated into the cascade impactor, Anderson Mark II cascade impactor (fig. 4.2), run at a flow rate of 28.7 L min⁻¹. The Rotahaler® was connected to the impactor by a rubberised, flexible, air tight ring (specially moulded). This fitted into a throat piece providing a 90° bend into the impactor. Each capsule was left in the impactor for 1 minute at the end of which each stage was washed with deionised water and made up to a volume of 10 ml. The solutions were then analysed for salbutamol sulphate content at 274 nm. The peak absorbance first being determined and the concentrations calculated using a predetermined absorbance calibration curve.

Similarly the twin impinger (fig. 4.1) was used to determine aerodynamic behaviour of the powders from the Rotahaler® (Glaxo) and the Spinhaler® (Fisons). One capsule at a time was analysed, liberated into the twin impinger running at an air flow rate of 60 L min⁻¹. Five ml of deionised water was placed at the base of stage one and 20 ml in the base of stage I. Deposits left in the device, stage I and stage II were collected by dissolving in deionised water and analysed by UV spectroscopy. Capsules containing an added carrier material, medium grade lactose or spray dried lactose, were also evaluated using the twin impinger. Six capsules of each type were tested. Capsules were liberated into the twin impinger at 60 L min⁻¹ and the second stage depositions analysed by fluorescence, (excitation wavelength, 224 nm and emission 316 nm) and expressed as percentage nominal salbutamol sulphate. The nominal being 400 µg (the dose in each capsule).
Preparation of the Capsules

To establish a sufficient mixing regime, mixing experiments were performed. Intermediate grade lactose and spray dried salbutamol sulphate were placed in a glass jar (size 24) in concentrations of 99.68% to 0.32% respectively (to give a concentration of 800 μg per 250 mg of mix). The jar was placed in a mixer, Turbula type T2C and mixed at a speed of 90 r.p.m. The mixture was sampled at 5, 10 and then every 10 minutes up to 70 minutes, in 9 positions (fig. 4.8), using a metal rod sampler (thief). Each sample was weighed, diluted and measured by UV at 274 nm, the salbutamol content was subsequently calculated as a percentage of the sample weight. The experiment was repeated using medium grade lactose, mixed at a speed of 42 r.p.m. It was discovered using the above experimentation and uniformity of dose measurements using fluorospectroscopy, that the best method for mixing was to mix the powders for 20 minutes, at a rate of 42 r.p.m., coarse sieve the powder (250 μm) and then remix for a further 20 minutes. This removes any agglomerates that may be present.

Figure 4.8 Sampling Positions For Mixing Experiment.
4.3 Results and Discussion

4.3.1 Particle Size, Size Distribution and Shape

Scanning Electron Microscope
Spray drying was seen to change the physical appearance of the powder particles from the needle-like structures, of the micronised salbutamol sulphate to spherical amorphous, sometimes pitted particles (Plates 2.4 and 2.5). From the electron micrographs it can be seen that the mean particle size of the spray dried material is between 1-3 μm and the approximately 5 μm for the micronised material. The size of the micronised salbutamol sulphate is difficult to determine due to the fact that the particles do not appear individually on the S.E.M.

Laser Diffraction
The size distribution results obtained from the Malvern Laser sizer for spray dried and micronised salbutamol sulphate are given in figures 4.9 and 4.11 respectively and are summarised in table 4.2. The size distribution of the spray dried material was seen to be narrower, having a median diameter of 4.4 μm and coefficient of spread (eqn. 4.) of 1.62, compared to that of the micronised which had median diameter of 4.7 μm and coefficient of spread of 1.72 (figs. 4.10 and 4.12).

\[
\text{Coefficient of Spread} = \frac{90\% \text{ (undersize)}}{\text{Median (50\%)}} \quad \text{Equation 4.12}
\]

Image Analysis
Figure 4.13 is a typical trace created by the image analyser created from the negative of the micrograph below (the digitise image definition of each particle created). The size (Feret’s diameter) distribution from the culmination of results obtained from several negatives is given in table 4.3
The shape of a particle was expressed as the variance in distance from the centre of mass to the periphery. Plates 4.1 and 4.2 show the assigned particles for the shape evaluation of spray dried and micronised salbutamol sulphate. Each particle being typical of the bulk of the powder. Figures 4.14 and 4.15 show the scatter plots of variance from the mean of the spray dried and micronised particles respectively. These results are summarised in table 4.2. The flatter the scatter plot the more spherical the particle. The elongated shape of the micronised particle is reflected by the two troughs seen on the plot (fig. 4.15).
### Chapter Four - Physico-Chemical Analysis

<table>
<thead>
<tr>
<th>Size (microns)</th>
<th>% under</th>
<th>Size band (microns)</th>
<th>%</th>
<th>Result source: Sample</th>
<th>Record No. = 0</th>
</tr>
</thead>
<tbody>
<tr>
<td>118.4</td>
<td>100.0</td>
<td>118.4 - 54.9</td>
<td>0.0</td>
<td>Focal length = 63 mm.</td>
<td></td>
</tr>
<tr>
<td>54.9</td>
<td>100.0</td>
<td>54.9 - 33.7</td>
<td>0.0</td>
<td>Experiment type oil</td>
<td></td>
</tr>
<tr>
<td>33.7</td>
<td>100.0</td>
<td>33.7 - 23.7</td>
<td>0.0</td>
<td>Volume distribution</td>
<td></td>
</tr>
<tr>
<td>23.7</td>
<td>100.0</td>
<td>23.7 - 17.7</td>
<td>0.0</td>
<td>Obscuration = 0.7835</td>
<td></td>
</tr>
<tr>
<td>17.7</td>
<td>100.0</td>
<td>17.7 - 13.6</td>
<td>0.1</td>
<td>Volume Conc. = 0.0141 %</td>
<td></td>
</tr>
<tr>
<td>13.6</td>
<td>99.9</td>
<td>13.6 - 10.5</td>
<td>0.6</td>
<td>Log. Diff. = 4.73</td>
<td></td>
</tr>
<tr>
<td>10.5</td>
<td>99.9</td>
<td>10.5 - 8.2</td>
<td>6.5</td>
<td>Model indp</td>
<td></td>
</tr>
<tr>
<td>8.0</td>
<td>100.0</td>
<td>8.2 - 6.4</td>
<td>7.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6.4</td>
<td>89.1</td>
<td>6.4 - 4.4</td>
<td>5.4</td>
<td>D(v,0,5) = 4.4 μm</td>
<td></td>
</tr>
<tr>
<td>5.0</td>
<td>87.0</td>
<td>5.4 - 5.0</td>
<td>22.1</td>
<td>D(v,6,9) = 6.5 μm</td>
<td></td>
</tr>
<tr>
<td>3.9</td>
<td>85.1</td>
<td>5.0 - 3.7</td>
<td>37.3</td>
<td>D(v,9,1) = 2.6 μm</td>
<td></td>
</tr>
<tr>
<td>2.4</td>
<td>3.9</td>
<td>3.7 - 2.4</td>
<td>5.7</td>
<td>D(4,3) = 4.6 μm</td>
<td></td>
</tr>
<tr>
<td>1.9</td>
<td>3.4</td>
<td>2.4 - 1.5</td>
<td>4.8</td>
<td>D(3,2) = 4.0 μm</td>
<td></td>
</tr>
<tr>
<td>1.5</td>
<td>1.3</td>
<td>1.5 - 1.2</td>
<td>2.1</td>
<td>Span = 0.9</td>
<td></td>
</tr>
<tr>
<td>1.2</td>
<td>0.8</td>
<td>1.2 - 0.5</td>
<td>0.5</td>
<td>Spec. surf. area</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 4.9 Size Distribution of Spray Dried Salbutamol Sulphate Measured by Laser Diffraction.**

**Figure 4.10 Cumulative Undersize/Oversize and Frequency Plot for Spray Dried Salbutamol Sulphate.**
<table>
<thead>
<tr>
<th>Size (μm)</th>
<th>% under</th>
<th>Size band (μm)</th>
<th>%</th>
<th>Result source</th>
<th>Sample</th>
<th>Record No.</th>
<th>Focal length</th>
<th>Beam length</th>
<th>Obscuration</th>
<th>Volume Conc.</th>
<th>Volume Cone.</th>
<th>Log. Diff.</th>
<th>Model indo</th>
<th>Spec. surf. area</th>
</tr>
</thead>
<tbody>
<tr>
<td>118.4</td>
<td>100.0</td>
<td>118.4 - 54.3</td>
<td>0.0</td>
<td>Sample</td>
<td>0</td>
<td>0</td>
<td>63</td>
<td>14.3</td>
<td>0.0019</td>
<td>0.0001</td>
<td>3.44</td>
<td>4.7</td>
<td>7.8</td>
<td>4.9</td>
</tr>
<tr>
<td>54.3</td>
<td>100.0</td>
<td>54.3 - 27.7</td>
<td>0.0</td>
<td>Sample</td>
<td>0</td>
<td>0</td>
<td>63</td>
<td>14.3</td>
<td>0.0019</td>
<td>0.0001</td>
<td>3.44</td>
<td>7.8</td>
<td>7.8</td>
<td>4.9</td>
</tr>
<tr>
<td>27.7</td>
<td>100.0</td>
<td>27.7 - 17.7</td>
<td>0.0</td>
<td>Sample</td>
<td>0</td>
<td>0</td>
<td>63</td>
<td>14.3</td>
<td>0.0019</td>
<td>0.0001</td>
<td>3.44</td>
<td>4.9</td>
<td>4.9</td>
<td>4.9</td>
</tr>
<tr>
<td>17.7</td>
<td>100.0</td>
<td>17.7 - 10.5</td>
<td>0.0</td>
<td>Sample</td>
<td>0</td>
<td>0</td>
<td>63</td>
<td>14.3</td>
<td>0.0019</td>
<td>0.0001</td>
<td>3.44</td>
<td>4.9</td>
<td>4.9</td>
<td>4.9</td>
</tr>
<tr>
<td>10.5</td>
<td>100.0</td>
<td>10.5 - 3.7</td>
<td>0.0</td>
<td>Sample</td>
<td>0</td>
<td>0</td>
<td>63</td>
<td>14.3</td>
<td>0.0019</td>
<td>0.0001</td>
<td>3.44</td>
<td>4.9</td>
<td>4.9</td>
<td>4.9</td>
</tr>
<tr>
<td>3.7</td>
<td>100.0</td>
<td>3.7 - 17.7</td>
<td>0.0</td>
<td>Sample</td>
<td>0</td>
<td>0</td>
<td>63</td>
<td>14.3</td>
<td>0.0019</td>
<td>0.0001</td>
<td>3.44</td>
<td>4.9</td>
<td>4.9</td>
<td>4.9</td>
</tr>
<tr>
<td>17.7</td>
<td>100.0</td>
<td>17.7 - 54.3</td>
<td>0.0</td>
<td>Sample</td>
<td>0</td>
<td>0</td>
<td>63</td>
<td>14.3</td>
<td>0.0019</td>
<td>0.0001</td>
<td>3.44</td>
<td>4.9</td>
<td>4.9</td>
<td>4.9</td>
</tr>
</tbody>
</table>

Figure 4.11 Size Distribution of Micronised Salbutamol Sulphate Measured by Laser Diffraction.

Figure 4.12 Cumulative Undersize/Oversize and Frequency Plot for Micronised Salbutamol Sulphate.
### Table 4.2 Particle Size Analysis of Spray Dried and Micronised Salbutamol Sulphate using Laser Diffraction.

<table>
<thead>
<tr>
<th>Sample</th>
<th>10%</th>
<th>50%</th>
<th>90%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spray Dried Salbutamol Sulphate</td>
<td>3.03 ± 1.05</td>
<td>4.78 ± 0.26</td>
<td>7.75 ± 0.84</td>
</tr>
<tr>
<td>Micronised Salbutamol Sulphate</td>
<td>2.6 ± 0.65</td>
<td>4.56 ± 1.33</td>
<td>7.86 ± 2.3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 4.3 Size Analysis of Spray Dried Salbutamol Sulphate Particles (823) using the Image Analyser.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum Particle Size (Feret’s diameter)</td>
</tr>
<tr>
<td>Minimum Particle Size (Feret’s diameter)</td>
</tr>
<tr>
<td>Mean Particle Size (Number average)</td>
</tr>
<tr>
<td>S.D.</td>
</tr>
</tbody>
</table>
Figure 4.13 Image Created by Image Analyser.
Plate 4.1 Particle of Micronised Salbutamol Sulphate
Assigned for Shape Analysis.

Plate 4.2 Particle of Spray Dried Salbutamol Sulphate
Assigned for Shape Analysis.
Figure 4.14 Scatter Plot Indicating Shape of Spray Dried Salbutamol Sulphate Particle.

Figure 4.15 Scatter Plot Indicating Shape of Micronised Salbutamol Sulphate Particle.
### Table 4.4 Shape Analysis Using Image Analyser.

<table>
<thead>
<tr>
<th></th>
<th>Mean Distance From Centre of Mass (μm)</th>
<th>Standard Deviation from Mean (μm)</th>
<th>Relative Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spray Dried Salbutamol Sulphate</td>
<td>0.8874</td>
<td>0.03393</td>
<td>3.8%</td>
</tr>
<tr>
<td>Micronised Salbutamol Sulphate</td>
<td>0.5896</td>
<td>0.3423</td>
<td>58.05%</td>
</tr>
</tbody>
</table>

The particle size distributions measured by laser diffraction and image analysis are different, as would be expected since different parameters were measured. Size and size distributions are dependent on the method of measurement employed (Neumann, 1967). Image analysis is a useful means of particle size measurement, the powders being measured directly without the need for suspension in another media. It does however have its limitations, these being mainly a function of sample preparation, this is very important since particles to be analysed must be discrete. Any particles overlapping may be counted as one, although these particles may be separated by manual manipulation of the trace, it is difficult. For particles that are not uniform in shape, analysis may become misleading unless the correct parameter for measurement is chosen. Laser techniques for measuring powders directly have been developed however, which may be a suitable alternative for size analysis (Blackford, 1987; Olsson et al, 1988, where a good correlation to impactor results was also noted). In summary spray drying was seen to produce particles that were within a suitable size range for inhalation, spherical and of a narrower size distribution than that of the micronised material.
4.3.2 Specific Surface Area

Specific surface area calculated by the Malvern laser sizer software from the volume distribution was seen to be larger, 1.54 m² cm⁻¹ (fig. 4.9) for the spray dried material compared to that of the micronised, 1.49 m² cm⁻¹ (fig. 4.11), as would be predicted from the particle shape and densities.

4.3.3 Density

The apparent density measured using the Beckman 930 air comparison pycnometer was found to be less for spray dried salbutamol sulphate than micronised salbutamol sulphate (table 4.5).

<table>
<thead>
<tr>
<th></th>
<th>Spray Dried Salbutamol Sulphate</th>
<th>Micronised Salbutamol Sulphate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apparent Density g cm⁻³</td>
<td>1.28</td>
<td>1.34</td>
</tr>
</tbody>
</table>

*Table 4.5 Density Measurements.*

The air comparison pycnometer has the advantage of being quick, accurate and not destroying the sample. There are two limitations to the accuracy (which is better than ± 0.1 cm⁻³), these being air leakage and heat transfer from or to the sample, both of which are immediately apparent as pointer drift when using the apparatus and therefore easily avoided.

4.3.4 Hollowness of Spray Dried Particles

None of the methods investigated yielded information concerning the hollowness of the spray dried spheres. Neither crushing between glass slides or grinding in a pestle caused fracturing of the particles. Difficulty of crushing small particles has been noted previously (Kendall, 1978). Araldite® adhesive was seen to dissolve the powder. Transmission electron microscopy (TEM) gave very little information even
at 200 Kv (Plate 4.3) as did freeze and fracture and freeze fracture (plate 4.4). Freeze fracture may be improved however, by use of an alternative solvent.
Plate 4.3 TEM Showing Spray Dried Salbutamol Sulphate (200 KV).

Plate 4.4 TEM Showing freeze fracture replicates of Spray dried salbutamol Sulphate.
4.3.5 X-Ray Diffraction

Figure 4.16 shows the powder X-ray diffraction profiles of both spray dried and micronised salbutamol sulphate.

![X-ray Diffraction Profiles](image)
Chapter Four - Physico-Chemical Analysis

It can be seen from the traces that spray drying caused a change in the crystallinity of salbutamol sulphate, making it more amorphous. This is in keeping with previous work concerned with the spray drying of other materials, which also showed a reduction in crystallinity (Matsuda et al, 1992; Vidgren et al, 1987c; Corrigan and Holohan, 1984; Corrigan et al, 1984).

4.3.6 Differential Scanning Calorimetry

Figure 4.17 is a typical DSC traces obtained for spray dried and micronised salbutamol sulphate. Figures 4.18 and 4.19 show the DSC peak analysis for both materials. These traces were reproducible. Spray dried material was seen to give sharper melting point compared to the micronised. In both cases however the melting point exceeds the reference value of 157-158° C (Merck Index, 1989) which may be a function of the pretreatment of the material. Micronisation may have caused glass states within the powder to exist. Batch to batch variation of the micronised material was seen to occur (fig. 4.20) which would suggest differences in milling procedure (e.g. milling time) may be the cause for the rise in melting point.

4.3.7 Potency

Fluorometric analysis showed spray dried salbutamol sulphate to have a potency of 95% when compared to the micronised material. The slight reduction in fluorescence may lead to reduction in pharmacological activity, further in vivo studies would be required however, to determine whether the effect is clinically important.
Figure 4.17 DSC Thermograms for (a) Spray Dried and (b) Micronised Salbutamol Sulphate.
Figure 4.18 DSC Thermogram Showing Peak Analysis for Spray Dried Salbutamol Sulphate.
Figure 4.19 DSC Thermogram Showing Peak Analysis for Micronised Salbutamol Sulphate.
Figure 4.20 DSC Thermogram for two Different Batches of Micronised Salbutamol Sulphate.
4.3.8 Infra Red Spectroscopy

Infra red spectra for spray dried and micronised salbutamol sulphate are given in figures 4.22 and 4.23 respectively. These compare favourably with the BP reference spectrum for salbutamol sulphate (fig. 4.23). Slight variations between the spectra are probably due to differences in crystallinity.

Figure 4.21 IR Spectrum for Salbutamol Sulphate (BP Reference Spectrum).
Figure 4.22 IR Spectrum for Spray Dried Salbutamol Sulphate.

Figure 4.23 IR Spectrum for Micronised Salbutamol Sulphate.
4.3.9 Powder Flow

Avicel/Aerosil mixtures proved to be a good model for flow characterisation. Aerosil, a known flow controlling agent (Handbook of Pharmaceutical Excipients) increased the flowability index of Avicel with increase in concentration up to a maximum concentration after which the flowability index decreased (table 4.6). As the concentration of Aerosil increases, the flow properties of the Aerosil become more prominent within the mixture, because Aerosil itself is a poor flowing powder the overall flowability decreases. Similar effects were noted with the addition of spray dried and micronised salbutamol sulphate to Avicel (tables 4.7 and 4.8). These are summarised in figure 4.24 where it can be seen that there is very little difference between the two forms of salbutamol sulphate. The flowability is noted to increase slightly with increase in salbutamol concentration, up to a maximum concentration of around 1% w/w after which the flow promoter effects decreased. Mixes of lactose and spray dried or micronised salbutamol followed the same pattern (tables 4.9 and 4.10 and fig. 4.25).

Powder characteristics of the spray dried and micronised salbutamol sulphate powders alone are given in table 4.11. The flowability of the spray dried material was poorer than that of the micronised. It should be noted however, that the flow measurements of these powders may not be as accurate as those of the mixtures as a consequence of the high cohesive forces that exist between particles of this size. For example the tapped density of the powder may be affected by cohesive nature and coarse sieving, which was preliminary to most of the flow measurements caused balling of the material on the sieve, in turn affecting other measurements.

In general the behaviour of the spray dried material was comparable to that of the micronised when mixed with other coarser diluents. However, when measured alone the flowability index for spray dried salbutamol sulphate was lower (31) than the index value for the micronised salbutamol sulphate (41). A possible reason for these observations may be due to the differences in hygroscopicity and hence the moisture content of the spray dried material. Previous work spray drying sodium cromoglycate
has shown an increase in powder hygroscopicity and hence decrease in powder stability (Vidgren et al, 1989). It should be noted that although comparative mixes were measured at the same time the total number of flow measurements were not all performed on the same day, therefore atmospheric conditions which were not controlled may have affected the powder flow.
<table>
<thead>
<tr>
<th>Material</th>
<th>Bulk density g cm$^{-3}$</th>
<th>Compressibility</th>
<th>Angle of repose</th>
<th>Angle of Spatula</th>
<th>Cohesion, Uniformity index</th>
<th>Flowability index</th>
<th>Degree of flowability</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Aerated</td>
<td>Packed</td>
<td>%</td>
<td>Index</td>
<td>Degree</td>
<td>Index</td>
<td>Index</td>
</tr>
<tr>
<td>Avicel</td>
<td>31.45</td>
<td>43.06</td>
<td>27.0</td>
<td>12</td>
<td>42</td>
<td>16</td>
<td>62</td>
</tr>
<tr>
<td></td>
<td>33.65</td>
<td>43.07</td>
<td>23.0</td>
<td>16</td>
<td>41</td>
<td>16</td>
<td>63</td>
</tr>
<tr>
<td>150g/ Aerosil</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.5g</td>
<td>32.34</td>
<td>42.79</td>
<td>24.4</td>
<td>16</td>
<td>41.5</td>
<td>16</td>
<td>59</td>
</tr>
<tr>
<td></td>
<td>32.17</td>
<td>42.44</td>
<td>24.0</td>
<td>16</td>
<td>38</td>
<td>18</td>
<td>59</td>
</tr>
<tr>
<td>Avicel</td>
<td>27.17</td>
<td>40.65</td>
<td>33.0</td>
<td>7</td>
<td>48</td>
<td>12</td>
<td>60</td>
</tr>
<tr>
<td>alone</td>
<td>26.43</td>
<td>40.32</td>
<td>34.0</td>
<td>7</td>
<td>47</td>
<td>12</td>
<td>63</td>
</tr>
</tbody>
</table>

*Table 4.6 Powder Flow Characteristics of Avicel/Aerosil Mixes.*
<table>
<thead>
<tr>
<th>Percentage</th>
<th>Bulk density g cm(^{-3})</th>
<th>Compressibility</th>
<th>Angle of repose</th>
<th>Flowability index</th>
<th>Degree of flowability</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Aerated</td>
<td>Packed</td>
<td>%</td>
<td>Index</td>
<td>Degree</td>
</tr>
<tr>
<td>0.00</td>
<td>27.11</td>
<td>40.65</td>
<td>33</td>
<td>7</td>
<td>48</td>
</tr>
<tr>
<td>0.50</td>
<td>26.92</td>
<td>41.59</td>
<td>35</td>
<td>7</td>
<td>47</td>
</tr>
<tr>
<td>0.75</td>
<td>27.38</td>
<td>42.42</td>
<td>35</td>
<td>7</td>
<td>47</td>
</tr>
<tr>
<td>1.00</td>
<td>27.73</td>
<td>41.94</td>
<td>34</td>
<td>7</td>
<td>44</td>
</tr>
<tr>
<td>2.00</td>
<td>27.12</td>
<td>41.78</td>
<td>35</td>
<td>7</td>
<td>46</td>
</tr>
<tr>
<td>5.00</td>
<td>29.07</td>
<td>44.53</td>
<td>35</td>
<td>7</td>
<td>47</td>
</tr>
</tbody>
</table>

Table 4.7 Powder Flow Characteristics of Avicell/Spray Dried Salbutamol Sulphate Mixes.
<table>
<thead>
<tr>
<th>Percentage Microsised Salbutamol Sulphate</th>
<th>Bulk density g cm$^{-3}$</th>
<th>Compressibility</th>
<th>Angle of repose</th>
<th>Angle of Spatula</th>
<th>Cohesion, Uniformity index</th>
<th>Flowability index</th>
<th>Degree of flowability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aerated</td>
<td>Packed</td>
<td>%</td>
<td>Index</td>
<td>Degree</td>
<td>Index</td>
<td>Degree</td>
<td>Index</td>
</tr>
<tr>
<td>0.00</td>
<td>27.17</td>
<td>40.65</td>
<td>33</td>
<td>7</td>
<td>48</td>
<td>12</td>
<td>60</td>
</tr>
<tr>
<td>0.50</td>
<td>27.64</td>
<td>41.97</td>
<td>34</td>
<td>7</td>
<td>49</td>
<td>12</td>
<td>68</td>
</tr>
<tr>
<td>0.75</td>
<td>28.24</td>
<td>41.93</td>
<td>33</td>
<td>7</td>
<td>43.5</td>
<td>16</td>
<td>69.5</td>
</tr>
<tr>
<td>1.00</td>
<td>28.26</td>
<td>42.15</td>
<td>33</td>
<td>7</td>
<td>47</td>
<td>12</td>
<td>65</td>
</tr>
<tr>
<td>2.00</td>
<td>29.38</td>
<td>43.68</td>
<td>33</td>
<td>7</td>
<td>46</td>
<td>17</td>
<td>66.5</td>
</tr>
<tr>
<td>5.00</td>
<td>28.95</td>
<td>43.74</td>
<td>34</td>
<td>7</td>
<td>49</td>
<td>12</td>
<td>67</td>
</tr>
</tbody>
</table>

Table 4.8 Powder Flow Characteristics of Avicel/Micronised Salbutamol Sulphate Mixes.
<table>
<thead>
<tr>
<th>Percentage Spray Dried Salbutamol Sulphate</th>
<th>Bulk density $g cm^{-3}$</th>
<th>Compressibility</th>
<th>Angle of repose</th>
<th>Angle of Spatula</th>
<th>Cohesion, Uniformity index</th>
<th>Flowability index</th>
<th>Degree of flowability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aerated</td>
<td>Packed</td>
<td>%</td>
<td>Index</td>
<td>Degree</td>
<td>Index</td>
<td>Degree</td>
<td>Index</td>
</tr>
<tr>
<td>0.00</td>
<td>66.50</td>
<td>89.84</td>
<td>26</td>
<td>14.5</td>
<td>40</td>
<td>18</td>
<td>57.5</td>
</tr>
<tr>
<td></td>
<td>66.54</td>
<td>90.82</td>
<td>27</td>
<td>12</td>
<td>39</td>
<td>18</td>
<td>59</td>
</tr>
<tr>
<td>0.25</td>
<td>70.63</td>
<td>90.94</td>
<td>22</td>
<td>16</td>
<td>40.5</td>
<td>17</td>
<td>59</td>
</tr>
<tr>
<td></td>
<td>70.88</td>
<td>91.99</td>
<td>23</td>
<td>16</td>
<td>41</td>
<td>17</td>
<td>57</td>
</tr>
<tr>
<td>0.50</td>
<td>63.64</td>
<td>82.98</td>
<td>23</td>
<td>16</td>
<td>39</td>
<td>19.5</td>
<td>59</td>
</tr>
<tr>
<td></td>
<td>64.12</td>
<td>82.34</td>
<td>22</td>
<td>16</td>
<td>43</td>
<td>18</td>
<td>55</td>
</tr>
<tr>
<td>1.00</td>
<td>71.98</td>
<td>93.24</td>
<td>23</td>
<td>16</td>
<td>37</td>
<td>18</td>
<td>52</td>
</tr>
<tr>
<td></td>
<td>73.33</td>
<td>88.32</td>
<td>17</td>
<td>18</td>
<td>41</td>
<td>17</td>
<td>55</td>
</tr>
<tr>
<td>2.00</td>
<td>72.32</td>
<td>92.65</td>
<td>22</td>
<td>16</td>
<td>41.5</td>
<td>16</td>
<td>62</td>
</tr>
<tr>
<td></td>
<td>71.40</td>
<td>92.90</td>
<td>23</td>
<td>16</td>
<td>42</td>
<td>16</td>
<td>62</td>
</tr>
<tr>
<td>5.00</td>
<td>65.48</td>
<td>86.31</td>
<td>24</td>
<td>16</td>
<td>41</td>
<td>17</td>
<td>61</td>
</tr>
<tr>
<td></td>
<td>65.16</td>
<td>86.35</td>
<td>24</td>
<td>16</td>
<td>41</td>
<td>17</td>
<td>60</td>
</tr>
</tbody>
</table>

*Table 4.9 Powder Flow Characteristics of Lactose/Spray Dried Salbutamol Sulphate Mixes.*
<table>
<thead>
<tr>
<th>Percentage Micronised Salbutamol Sulphate</th>
<th>Bulk density g cm⁻³</th>
<th>Compressibility</th>
<th>Angle of repose</th>
<th>Angle of Spatula</th>
<th>Cohesion, Uniformity index</th>
<th>Flowability index</th>
<th>Degree of flowability</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00</td>
<td>Aerated 66.50</td>
<td>Packed 89.84</td>
<td>26</td>
<td>14.5</td>
<td>40</td>
<td>18</td>
<td>57.5</td>
</tr>
<tr>
<td></td>
<td>66.54</td>
<td>90.82</td>
<td>27</td>
<td>12</td>
<td>39</td>
<td>18</td>
<td>59</td>
</tr>
<tr>
<td>0.25</td>
<td>70.03</td>
<td>88.40</td>
<td>21</td>
<td>17</td>
<td>37</td>
<td>18</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td>69.96</td>
<td>88.74</td>
<td>21</td>
<td>17</td>
<td>37</td>
<td>18</td>
<td>56</td>
</tr>
<tr>
<td>0.50</td>
<td>72.78</td>
<td>90.68</td>
<td>20</td>
<td>18</td>
<td>39</td>
<td>18</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td>72.68</td>
<td>90.28</td>
<td>20</td>
<td>18</td>
<td>38</td>
<td>18</td>
<td>55</td>
</tr>
<tr>
<td>1.00</td>
<td>73.04</td>
<td>88.28</td>
<td>17</td>
<td>18</td>
<td>39</td>
<td>18</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>73.33</td>
<td>88.32</td>
<td>17</td>
<td>18</td>
<td>41</td>
<td>17</td>
<td>55</td>
</tr>
<tr>
<td>2.00</td>
<td>65.55</td>
<td>88.95</td>
<td>26</td>
<td>15</td>
<td>38</td>
<td>18</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td>66.55</td>
<td>88.61</td>
<td>26</td>
<td>14.5</td>
<td>38</td>
<td>18</td>
<td>55</td>
</tr>
<tr>
<td>5.00</td>
<td>65.48</td>
<td>86.31</td>
<td>24</td>
<td>16</td>
<td>41</td>
<td>17</td>
<td>61</td>
</tr>
<tr>
<td></td>
<td>65.16</td>
<td>86.35</td>
<td>24</td>
<td>16</td>
<td>41</td>
<td>17</td>
<td>60</td>
</tr>
</tbody>
</table>

Table 4.10 Powder Flow Characteristics of Lactose/Micronised Salbutamol Sulphate.
<table>
<thead>
<tr>
<th>Material</th>
<th>Bulk density g cm⁻¹</th>
<th>Compressibility</th>
<th>Angle of repose</th>
<th>Angle of Spatula</th>
<th>Cohesion Index</th>
<th>Flowability index</th>
<th>Degree of Flowability</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Aerated</td>
<td>Packed</td>
<td>%</td>
<td>Index</td>
<td>Degree</td>
<td>Index</td>
<td>Total</td>
</tr>
<tr>
<td>Spray Dried Salbutamol Sulphate</td>
<td>25.76</td>
<td>50.85</td>
<td>49.3</td>
<td>0</td>
<td>41</td>
<td>17</td>
<td>61</td>
</tr>
<tr>
<td></td>
<td>26.65</td>
<td>54.17</td>
<td>50.8</td>
<td>0</td>
<td>39</td>
<td>18</td>
<td>64</td>
</tr>
<tr>
<td>Micronised Salbutamol Sulphate</td>
<td>16.7</td>
<td>26.66</td>
<td>37.4</td>
<td>5</td>
<td>36.5</td>
<td>19.5</td>
<td>59</td>
</tr>
<tr>
<td></td>
<td>17.36</td>
<td>27.01</td>
<td>35.72</td>
<td>7</td>
<td>41</td>
<td>17</td>
<td>60</td>
</tr>
</tbody>
</table>

*Table 4.11 Powder Flow Characteristics of Spray Dried and Micronised Salbutamol Sulphate.*
Figure 4.24 The Influence of Spray Dried and Micronised Salbutamol Sulphate on the Flowability Index of Avicel.

Figure 4.25 The Influence of Spray Dried and Micronised Salbutamol Sulphate on the Flowability Index of Medium Grade Lactose.
### 4.3.10 Powder Mixing

An adequate mix was considered to be accomplished when the smallest standard deviation, of salbutamol content, between samples was achieved. Using equation 4.13 it can be seen that a standard deviation of 0.017% would give a uniform mix whereby 95% of the samples lie within ± 10% of the mean, this was achieved at 40 minutes (fig. 4.28).

\[
\text{S.D.} = 0.05x \quad \text{Equation 4.13}
\]

Where S.D.= standard deviation and x=mean (Crooks and Ho, 1976)

Problems occurred with the experimental technique used. Lactose was found to affect UV absorbance at 274 nm, the salbutamol sulphate maxima. It can be seen from the UV trace (fig. 4.26) that lactose absorbs in this region. The effect on absorbance of salbutamol sulphate measured was to give consistently higher readings than would be expected. The effect of lactose was noted to be linear with increase in concentration (fig. 4.27). It is this effect that caused an increased in UV determined final percentage salbutamol sulphate in the lactose/salbutamol sulphate mix. Taking this finding into consideration it was found that mixing at a slower speed 42 r.p.m. for 30-40 minutes was sufficient to produce adequate mixing (fig 4.28). Deaggregation seen after this time is probably caused by aggregate formation by salbutamol sulphate particles or dissociation of the particles from their sites, (Staniforth, 1982). However, when filled in capsules the uniformity of dose between capsules was found to be poor (table 4.12). Correct mixing should have produced capsules each containing 400µg of salbutamol sulphate. The method finally adopted was to mix the powders for 20 minutes, coarse sieve the mixture and then mix for a further 20 minutes. This improved the uniformity of content (table 4.13) and was thought to be a consequence of deaggregation of any large clumps of salbutamol sulphate formed during the mixing procedure.
Figure 4.26 UV Absorbance Spectrum for Lactose.
Figure 4.27 The Effect of Lactose Concentration on the UV Absorbance of a 0.01% Solution of Salbutamol Sulphate (Correlation coefficient 0.93).

Figure 4.28 The Effect of Mixing Time on Salbutamol Sulphate/Lactose mix

(a) 90 r.p.m., (b) 42 r.p.m.
### Table 4.12 Uniformity of Capsule Content (Unsieved powder).

<table>
<thead>
<tr>
<th>Batch</th>
<th>Salbutamol Sulphate Content (μg)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Range</td>
<td>% RSD</td>
</tr>
<tr>
<td><strong>Lactose/Spray Dried Salbutamol</strong></td>
<td>295.3</td>
<td>270.1-329.7</td>
<td>9.2</td>
</tr>
<tr>
<td><strong>Lactose/ Micronised Salbutamol</strong></td>
<td>420.9</td>
<td>357.4-567.2</td>
<td>18.1</td>
</tr>
<tr>
<td><strong>Spray Dried Lactose/ Spray Dried Salbutamol Sulphate</strong></td>
<td>355.9</td>
<td>323.8-443.3</td>
<td>12.2</td>
</tr>
<tr>
<td><strong>Spray Dried Lactose/ Micronised Salbutamol Sulphate</strong></td>
<td>435.6</td>
<td>316.1-786.4</td>
<td>40.3</td>
</tr>
</tbody>
</table>

### Table 4.13 Uniformity of Capsule Content (sieved powder).

<table>
<thead>
<tr>
<th>Batch</th>
<th>Salbutamol Sulphate Content (μg)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Range</td>
<td>% RSD</td>
</tr>
<tr>
<td><strong>Lactose/Spray Dried Salbutamol Sulphate</strong></td>
<td>356.8</td>
<td>337.0-383.0</td>
<td>4.7</td>
</tr>
<tr>
<td><strong>Lactose/ Micronised Salbutamol Sulphate</strong></td>
<td>391.6</td>
<td>371.4-416.9</td>
<td>4.5</td>
</tr>
<tr>
<td><strong>Spray Dried Lactose/ Spray Dried Salbutamol Sulphate</strong></td>
<td>348.5</td>
<td>341.6-352.9</td>
<td>1.3</td>
</tr>
<tr>
<td><strong>Spray Dried Lactose/ Micronised Salbutamol Sulphate</strong></td>
<td>318.8</td>
<td>311.2-334.0</td>
<td>3.0</td>
</tr>
</tbody>
</table>

Chapter Four - Physico-Chemical Analysis
Homogeneity of a mix can be influenced by mainly factors including, bond strength between particles, surface roughness (Staniforth et al, 1982) particle shape, powder flow (Wong and Pilpel, 1990), particle size (Crooks and Ho, 1976) and particle size distribution of both the carrier and the drug. The wider the size distribution the more likely segregation will occur, resulting in non-representative particle sampling, (Thanomkiat et al, 1979). The lactose powder size distribution are given in Appendix 3. When drug particles are as small, in this case, the likely mechanism for mixing is one of an ordered mix (Hersey, 1975), where particle-particle interactions occur as a consequence of the drug adhering to the carrier. The difficulty with mixing this type of formulation is that the cohesive forces between the drug particles need to be broken before adhesional forces can be formed (Nystrom and Malmqvist, 1980). The Turbula T2C mixer acts mainly by diffusive mixing and to some extent shear mixing (Nystrom and Malmqvist, 1980). The reason for poor capsule uniformity without sieving may therefore have been caused by the inability of the Turbula mixer alone to disrupt the interparticulate cohesive forces. An alternative mixer that mixes by shearing as the main mechanism may have been more efficient in this case.

The disadvantage of this method of mixing is that losses of salbutamol sulphate can occur. The difficulty in efficient capsule preparation lies in the small scale mixing procedure and the manual capsule filling.
4.3.11 In Vitro Deposition

Twin Impinger

Results from the inertial impaction studies using the twin impinger are given in tables 4.14 for spray dried and micronised salbutamol sulphate liberated from the Rotahaler®. Table 4.15 shows percentage deposition when liberated from the Spinhaler®.

<table>
<thead>
<tr>
<th>Sample</th>
<th>Percentage Weight (average ± S.D, n=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Device</td>
</tr>
<tr>
<td>Spray Dried Salbutamol Sulphate</td>
<td>45.48 ± 5.80</td>
</tr>
<tr>
<td>Micronised Salbutamol Sulphate</td>
<td>47.35 ± 1.35</td>
</tr>
</tbody>
</table>

*Table 4.14 Twin Impinger Analysis of Spray Dried and Micronised Salbutamol Sulphate Liberated from the Rotahaler®*

<table>
<thead>
<tr>
<th>Sample</th>
<th>Percentage Weight (average ± S.D, n=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Device</td>
</tr>
<tr>
<td>Spray Dried Salbutamol Sulphate</td>
<td>37.73 ± 8.12</td>
</tr>
<tr>
<td>Micronised Salbutamol Sulphate</td>
<td>43.24 ± 7.60</td>
</tr>
</tbody>
</table>

*Table 4.15 Twin Impinger Analysis of Spray Dried and Micronised Salbutamol Sulphate Liberated from the Spinhaler®*
Using the stage II percentage weights for comparison spray dried salbutamol liberated more readily from the Spinhaler® device. There was little difference between deposition of the micronised and spray dried drug when using the Spinhaler®. The probability of stage II deposition being the same for both spray dried and micronised salbutamol sulphate was $P=0.5$ (calculated using the T-Test where $T=0.74$ and degrees of freedom=4). In the case of the Rotahaler® however, the percentage weight deposited in the second stage was higher for the micronised material, the probability of stage II deposition being the same was $P=0.0005$ ($T=10.46$ and degrees of freedom=4).

When mixed with a carrier material the results were found to be poorer (table 4.16). It would be expected that the micronised drug would be less likely to deaggregate from the lactose, being more variable in shape and having more points for contact with the carrier, (Wong and Pilpel, 1990).

<table>
<thead>
<tr>
<th>Batch</th>
<th>% Nominal Salbutamol Sulphate Found in Stage II (Nominal 400 µg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
</tr>
<tr>
<td>Lactose/Spray Dried Salbutamol Sulphate</td>
<td>2.4</td>
</tr>
<tr>
<td>Lactose/ Micronised Salbutamol Sulphate</td>
<td>5.5</td>
</tr>
<tr>
<td>Spray Dried Lactose/ Spray Dried Salbutamol Sulphate</td>
<td>0.4</td>
</tr>
<tr>
<td>Spray Dried Lactose/ Micronised Salbutamol Sulphate</td>
<td>0.5</td>
</tr>
<tr>
<td>Ventolin Rotacaps® (Lot. 50851)</td>
<td>16.8</td>
</tr>
</tbody>
</table>

*Table 4.16 Stage II Twin Impinger Analysis of Drug with Carrier, Liberated from a Rotahaler®.*
A possible explanation for this may lie with the hygroscopicity of the two materials or the particle size which was seen using S.E.M. to be much smaller, smaller particles have been noted to adsorb more efficiently to carrier materials (Schmidt and Benke, 1985). Separation of both the micronised and spray dried drug from spray dried lactose was seen to be very poor. This is probably a consequence of the higher surface free energy of spray dried lactose compared to that of the medium grade lactose (see chapter 5). It should be noted that the spray dried lactose is not totally spherical, but consists of a mixture of spheres and crystalline structures because it is spray dried as a slurry rather than a solution. Therefore the change in crystallinity is not great. Spray drying lactose as a solution may however alter its surface free energy properties making it a more suitable carrier.

Results are very dependent on both the carrier and the liberating device. The spinhaler has previously been shown to be dependent on the DPI formulation (section 1.3.2). Results using a new liberation device manufactured by Rhône-Poulenc Rorer Ltd., (Patent application no. WO'91/19524), substantiate this (table 4.17).
### Table 4.17 Stage II Twin Impinger Analysis of Drug with Carrier, Liberated from a Novel Delivery Device (Patent Application No. WO'91119524).

<table>
<thead>
<tr>
<th>Batch</th>
<th>% Nominal Salbutamol Sulphate Found in Stage II (Nominal 400 µg)</th>
<th>Mean</th>
<th>Range</th>
<th>% RSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactose/Spray Dried Salbutamol Sulphate</td>
<td></td>
<td>15.3</td>
<td>14.1-17.8</td>
<td>8.4</td>
</tr>
<tr>
<td>(0.3%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactose/ Micronised Salbutamol Sulphate</td>
<td></td>
<td>23.8</td>
<td>17.9-28.5</td>
<td>15.2</td>
</tr>
<tr>
<td>(0.3%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spray Dried Lactose/ Spray Dried Salbutamol Sulphate</td>
<td></td>
<td>1.6</td>
<td>0.4-3.8</td>
<td>73.5</td>
</tr>
<tr>
<td>(0.3%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spray Dried Lactose/ Micronised Salbutamol Sulphate</td>
<td></td>
<td>7.7</td>
<td>3.0-13.4</td>
<td>59.8</td>
</tr>
<tr>
<td>(0.3%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventolin Rotacaps</td>
<td></td>
<td>32.5</td>
<td>28.5-39.6</td>
<td>12.7</td>
</tr>
</tbody>
</table>

It should be noted however, that the uniformity of dose for these capsules were poor, also for results given in both tables 4.16 and 4.17 that the fluorometric potency of spray dried salbutamol was 95% that of the micronised. The proprietary preparation, (Rotacaps®) in each case gave better deposition results this may have been caused by a number of factors; the method of capsule preparation in this study was crude, leading to drug losses and consequently poor capsule uniformity. The Rotacaps® are prepared containing lactose of a known, narrow size distribution giving optimum flow and are specially formulated for the Rotahaler®. The medium grade lactose in this case may not have been optimum for the drug to flow efficiently (Appendix 3). Fluorometry showed the activity of the spray dried material to be less than that of the
micronised (the comparative fluorescence of the material in the Rotacaps however was unknown).

**Cascade Impactor**

The results from aerodynamic particle size analysis using the cascade impactor of spray dried salbutamol sulphate, micronised salbutamol sulphate and a proprietary preparation (Ventolin Rotacaps®) are given in tables 4.18, 4.19 and 4.20 respectively. The results show that deposition at stage 3 and below was greatest for the Rotacaps, followed by the micronised drug and the spray dried drug respectively. This is in keeping with the results obtained using the twin impinger. The MMADs obtained however are similar for all three preparations (table 4.21), but do not correspond well to the sizing performed using the image analyser or laser diffraction. MMAD calculated, using data obtained from the laser diffraction and density measurement (air comparison pycnometer) gave MMADs of 5.41 μm and 5.27 μm for spray dried and micronised salbutamol sulphate. The differences between the MMAD values obtained is probably a consequence of the different methods of analysis used and also may be due to incomplete deaggregation of the powders in the impactor, the MMAD thus representing aggregates rather than individual particles. There are several limitations to the cascade impinger analysis, the operational air flow rate may not be sufficient to break up any aggregates that may be present, the UV analysis of the Ventolin Rotacaps® may be falsely high due to lactose absorbance around the absorbance maximum, mentioned above. However the percentage of lactose is small and may not be important.
<table>
<thead>
<tr>
<th>Stage</th>
<th>Average % wt per stage (n=4)</th>
<th>S.D.</th>
<th>Cumulative % undersize</th>
<th>Size Range (μm)</th>
<th>ECD (μm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Throat</td>
<td>38.33</td>
<td>4.85</td>
<td>61.17</td>
<td>≥10.0</td>
<td>≥10.0</td>
</tr>
<tr>
<td>0</td>
<td>44.02</td>
<td>1.70</td>
<td>17.15</td>
<td>9.0-10.0</td>
<td>9.0</td>
</tr>
<tr>
<td>1</td>
<td>8.05</td>
<td>2.30</td>
<td>9.10</td>
<td>5.8-9.0</td>
<td>5.8</td>
</tr>
<tr>
<td>2</td>
<td>5.09</td>
<td>1.84</td>
<td>4.01</td>
<td>4.7-5.8</td>
<td>4.7</td>
</tr>
<tr>
<td>3</td>
<td>1.56</td>
<td>0.69</td>
<td>2.45</td>
<td>3.3-4.7</td>
<td>3.3</td>
</tr>
<tr>
<td>4</td>
<td>0.42</td>
<td>0.12</td>
<td>2.03</td>
<td>2.1-3.3</td>
<td>2.1</td>
</tr>
<tr>
<td>5</td>
<td>0.49</td>
<td>0.62</td>
<td>1.54</td>
<td>1.1-2.1</td>
<td>1.1</td>
</tr>
<tr>
<td>6</td>
<td>0.08</td>
<td>0.039</td>
<td>1.46</td>
<td>0.7-1.1</td>
<td>0.7</td>
</tr>
<tr>
<td>7</td>
<td>0.08</td>
<td>0.042</td>
<td>1.38</td>
<td>0.4-0.7</td>
<td>0.4</td>
</tr>
<tr>
<td>Filter</td>
<td>1.38</td>
<td>0.63</td>
<td>0</td>
<td>0-0.4</td>
<td>0</td>
</tr>
</tbody>
</table>

*Tables 4.18 Cascade Impactor Analysis of Spray Dried Salbutamol Sulphate Delivered from the Rotahaler®.*
<table>
<thead>
<tr>
<th>Stage</th>
<th>Average % wt per stage (n=4)</th>
<th>S.D.</th>
<th>Cumulative % Undersize</th>
<th>Size Range (µm)</th>
<th>ECD (µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Throat</td>
<td>24.10</td>
<td>4.84</td>
<td>75.44</td>
<td>≥10.0</td>
<td>10.0</td>
</tr>
<tr>
<td>0</td>
<td>50.91</td>
<td>7.86</td>
<td>24.53</td>
<td>9.0-10.0</td>
<td>9.0</td>
</tr>
<tr>
<td>1</td>
<td>10.59</td>
<td>6.53</td>
<td>13.94</td>
<td>5.8-9.0</td>
<td>5.8</td>
</tr>
<tr>
<td>2</td>
<td>6.22</td>
<td>2.64</td>
<td>7.72</td>
<td>4.7-5.8</td>
<td>4.7</td>
</tr>
<tr>
<td>3</td>
<td>2.83</td>
<td>1.15</td>
<td>4.89</td>
<td>3.3-4.7</td>
<td>3.3</td>
</tr>
<tr>
<td>4</td>
<td>0.67</td>
<td>0.36</td>
<td>4.22</td>
<td>2.1-3.3</td>
<td>2.1</td>
</tr>
<tr>
<td>5</td>
<td>0.77</td>
<td>0.97</td>
<td>3.45</td>
<td>1.1-2.1</td>
<td>1.1</td>
</tr>
<tr>
<td>6</td>
<td>0.10</td>
<td>0.02</td>
<td>3.35</td>
<td>0.7-1.1</td>
<td>0.7</td>
</tr>
<tr>
<td>7</td>
<td>0.08</td>
<td>0.03</td>
<td>3.27</td>
<td>0.4-0.7</td>
<td>0.4</td>
</tr>
<tr>
<td>Filter</td>
<td>3.27</td>
<td>4.17</td>
<td>0</td>
<td>0-0.4</td>
<td>0</td>
</tr>
</tbody>
</table>

Tables 4.19 Cascade Impactor Analysis of Micronised Salbutamol Sulphate Delivered from the Rotahaler®.
<table>
<thead>
<tr>
<th>Stage</th>
<th>Average % wt per stage (n=4)</th>
<th>S.D</th>
<th>Cumulative % undersize</th>
<th>Size Range (µm)</th>
<th>ECD (µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Throat</td>
<td>31.39</td>
<td>.80</td>
<td>68.60</td>
<td>≥10.0</td>
<td>10.0</td>
</tr>
<tr>
<td>0</td>
<td>21.45</td>
<td>4.70</td>
<td>47.15</td>
<td>9.0-10.0</td>
<td>9.0</td>
</tr>
<tr>
<td>1</td>
<td>6.25</td>
<td>0.82</td>
<td>40.90</td>
<td>5.8-9.0</td>
<td>5.8</td>
</tr>
<tr>
<td>2</td>
<td>4.37</td>
<td>0.34</td>
<td>36.53</td>
<td>4.7-5.8</td>
<td>4.7</td>
</tr>
<tr>
<td>3</td>
<td>5.01</td>
<td>0.08</td>
<td>31.52</td>
<td>3.3-4.7</td>
<td>3.3</td>
</tr>
<tr>
<td>4</td>
<td>3.96</td>
<td>1.68</td>
<td>27.56</td>
<td>2.1-3.3</td>
<td>2.1</td>
</tr>
<tr>
<td>5</td>
<td>1.72</td>
<td>0.76</td>
<td>25.84</td>
<td>1.1-2.1</td>
<td>1.1</td>
</tr>
<tr>
<td>6</td>
<td>1.44</td>
<td>0.62</td>
<td>24.40</td>
<td>0.7-1.1</td>
<td>0.7</td>
</tr>
<tr>
<td>7</td>
<td>1.18</td>
<td>0.26</td>
<td>23.22</td>
<td>0.4-0.7</td>
<td>0.4</td>
</tr>
<tr>
<td>Filter</td>
<td>23.22</td>
<td>5.48</td>
<td>0</td>
<td>0-0.4</td>
<td>0</td>
</tr>
</tbody>
</table>

*Tables 4.20 Cascade Impactor Analysis of a Proprietary (Ventolin Rotacaps®) Salbutamol Sulphate Delivered from the Rotahaler®.*
Chapter Four - Physico-Chemical Analysis

<table>
<thead>
<tr>
<th>Material</th>
<th>MMAD, μm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spray Dried Salbutamol Sulphate</td>
<td>9.7</td>
</tr>
<tr>
<td>Micronised Salbutamol Sulphate</td>
<td>9.6</td>
</tr>
<tr>
<td>Proprietary Preparation (Rotacaps)</td>
<td>9.8</td>
</tr>
</tbody>
</table>

Table 4.21 Mass Mean Aerodynamic Diameters, From Cascade Impactor Analysis.

4.4 Conclusions

Spray drying of salbutamol sulphate produced particles within a narrow size distribution, having a mean particle size, suitable for delivery to the respiratory tract, measured by laser diffraction, S.E.M and image analysis. Spray drying was not seen to destroy the activity of the salbutamol (fluorospectroscopy), nor change it chemically, shown by infra red spectroscopy. The crystallinity and the differential scanning calorimetric thermograms were however, altered. Spray drying produced amorphous powders, shown by powder X-ray diffraction.

Physically, the powder particle shape altered to give spheres, demonstrated by the S.E.M. and by shape analysis using the image analyser, the density was reduced and the compressibility increased, the bulk density being greater. Flow measurements showed spray dried salbutamol sulphate to perform in a similar manner to that of the micronised material when mixed with coarse diluents, such as Avicel and lactose. When the spray dried and micronised drug were measured alone, both had poor flowability, the flowability of the spray dried drug however, was seen to be the poorer of the two.

The flowability measurements explained the results obtained from the in vitro deposition studies, where it was noted the deposition in the in vitro pulmonary regions was seen to be the same or poorer than that of the micronised drug. It was found that the formulation and the liberation device effected deposition, this is in keeping with
previous work in this area (section 1.3.2). The behaviour with different types of lactose could be predicted by the free surface energies associated with each type (Chapter 5). Using two different in vitro deposition techniques, the twin impinger and the cascade impactor, confirmed previous findings that the twin impinger distinguishes more clearly between formulations, however, this may be a consequence of the higher operational flow rate. Spray dried, micronised and the proprietary salbutamol sulphate formulations were all seen to have similar MMAD when analysed using the cascade impactor.
Chapter Five
Surface Energetics
Surface Energetics

5.1 Introduction
The free energy of a material surface is dependent on both its chemical nature, related to its molecular structure, and its physical treatment (Buckton, 1990). The surface energy and the polarity of a material play an important part in its behaviour and interaction with other phases. As a consequence surface energy and polarity measurements have been used as predictors of interactions, between phases, for use in pharmaceutical formulation. For example surface energies have been used in the choice of binder for use in wet granulation (Zajic and Buckton, 1990), for prediction of tablet properties from drug binder interactions (Rowe, 1990), tensile strength of powder compacts (El Gindy and Samaha, 1983), in suspension formulation for prediction of aggregation (Young and Buckton, 1990) and stability of non polar, non aqueous suspensions (Parsons et al, 1992).

The physical pre-treatment of a powder, such as size reduction by milling, crystallisation or controlled precipitation, will affect the surface morphology and characteristics and hence its surface energy which is reflected by contact angle measurement (Lerk et al, 1976; Hansford et al, 1980). Where milling is concerned the total history of the powder is important. Buckton et al (1988) showed that different milling techniques and the cumulative effect of milling by two successively different techniques effected the surface energy of aspirin. Where more than one milling process was performed, the first played a greater part than the second, in the final surface energy. This was thought to be a consequence of the second comminution process acting upon the flaws created by the first, rather than the creation of totally new surfaces.

Powders used for dry powder aerosol formulation need to be of a small particle size, ideally having a mass medium aerodynamic diameter of ≤ 10 μm for pulmonary delivery (Gonda and Byron, 1978) and around 5 μm for bronchial (peripheral) deposition (Matthys, 1990). Powders comprising of particles in this size order are
renowned for being difficult to formulate as a consequence of the high cohesive and adhesive forces of the particles (Neumann, 1967). The powders tend to be poorly flowing (section 4.3.9) and adhere to surfaces, a property that was observed experimentally (section 4.3.11) where a large percentage of the spray dried and micronised salbutamol sulphate adhered to the aerosol liberation device on actuation in twin impinger analysis (tables 4.14 and 4.15). The cohesive and adhesive nature of a powder is reflected by its surface energy and polarity. By measurement of powder surface energies and polarities of the spray dried and micronised salbutamol sulphate, it is proposed that differences in material behaviour can be predicted and compared to experimental results.

5.1.1 Contact Angle Measurement

The surface free energy of a powder cannot be measured directly, but can be calculated from contact angle measurement (Zografi and Tam, 1976; Kloubek, 1992). Contact angle (θ) measurement with smooth polymeric systems is relatively simple. However, powders do not possess smooth surfaces and therefore contact angle measurements must be made indirectly. Several methods are used for indirect contact angle measurement which include; liquid penetration, measurements using compressed powder discs and the Wilhelmy gravitational method, all of which have been reviewed by Buckton (1990).

**Liquid Penetration**

This method involves the comparison of rate of penetration of two liquids into a loosely packed powder bed. One of the liquids is known to be perfectly wetting whilst the other, the test liquid, is the liquid for which the contact angle is required. The contact angle is calculated using a formula derived by Studebaker and Snow (1955) (eqn. 5.1) which is based on the Washburn equation (eqn. 5.2) (1921), for liquid penetration through a horizontal capillary, under its own capillary pressure.
Chapter 5 - Surface Energetics

\[ \cos \theta = \frac{\eta_I \gamma_{II} \text{Gradient}_{II}}{\eta_{II} \gamma_I \text{Gradient}_I} \]  
\text{Equation 5.1}

\[ l^2 = r \gamma_{lv} \frac{\cos \theta t}{2\eta} \]  
\text{Equation 5.2}

Where \( \eta \) is the viscosity, gradient is the gradient of the plot of distance of penetration \( l \) squared as a function of time, \( I \), represents the perfectly wetting liquid and \( II \), the test liquid, \( \theta \) is the contact angle, \( t \) is time, \( r \) is the capillary radius of the bed (it is assumed that the bed is made up of a bundle of parallel capillaries) and \( \gamma_{lv} \) is the liquid/vapour interfacial energy.

There are several criticisms of this method:

i) The hydrophobicity of a powder may interfere with measurements. If a powder is very hydrophobic the liquid, if polar e.g. water, will not penetrate the powder bed (Buckton and Newton, 1985). This problem has been overcome by the use of water/alcohol mixtures (the results from which are extrapolated back to give the theoretical water value). This however, has the potential disadvantage of solvent separation during powder bed penetration (Good, 1977) and, as predicted by Raoults' law, the vapour that precedes the liquid will be preferentially rich in alcohol thus removing the basis for extrapolation to water (Buckton, 1988).

ii) It has been questioned that distance of penetration squared as a function of time could be predicted by bed porosity (Yang et al, 1988).

iii) Perfectly wetting liquids are difficult to find (Luangtana-anan and Fell, 1988), this is overcome by using the best wetting liquid (Buckton and Newton, 1985)

iv) The Washburn equation has been questioned, the penetration distance should not always be raised to the power of two (Heertjes and Kossen, 1967; Carli and Simioni, 1979).
Despite all the above criticisms the results obtained by this method compare favourably to plate techniques up to contact angles of 70° (Yang et al, 1988), above which liquid penetration experiments give larger angles. This method is useful for qualitative powder wettability ranking (Buckton, 1990), especially where the powders under investigation are to be used in their non compressed form (Buckton and Newton, 1985), but is of limited value when assessing the surface energy parameters of non compacted powders, as a result of its many theoretical shortcomings (Buckton and Newton, 1986a).

**Contact Angle Measurement Using Compressed Discs**

This method involves the observation of a liquid drop on the surface of a compacted powder disc. The powders in question are formed into compacted discs and usually, pre-saturated with the test liquid. A drop of the test liquid is then formed on the disc surface and the angle formed measured directly using a protractor eye piece mounted on a goniometer or by photographing the drop and measuring the angle on the print.

An alternative method is that of the h-e method, whereby a drop of maximum height is created on the surface and the height measured. The contact angle can then be calculated using equations developed by Kossen and Heertjes (1965) for contact angles between 0° and 90° (eqn. 5.3) and for angles above 90° (eqn. 5.4). This method compares well with that of direct measurement.

\[
\cos \theta = 1 - \sqrt{\frac{(Bh)^2}{3(1-z)(1-B(h)^2/2)}} \quad \text{Equation 5.3}
\]

\[
\cos \theta = -1 + \sqrt{\frac{2}{3(1-z)}} \left( \frac{2}{Bh^2} - 1 \right) \quad \text{Equation 5.4}
\]

Where \(h\)=maximum height of the drop, \(z\)= volume porosity and \(B\)= equation 5.5
Chapter 5 - Surface Energetics

\[ B = \frac{\rho g}{2\gamma_{lv}} \]

Equation 5.5

Where \( \rho \) = the density of the liquid, \( g \) = the acceleration due to gravity and \( \gamma_{lv} \) = the liquid/vapour interfacial energy.

There are several criticisms of this method:

i) The powders have to be compressed into discs before measurement. It has been shown that compression may alter the surface structure of the powder, by plastic deformation and therefore contact angle measurement may not be a true reflection of the bulk of the powder (Buckton and Newton, 1986b).

ii) The discs produced must be smooth, rough surfaces may lead to hysteresis (that is, changes in advancing and receding angles) and consequently unreliable results. The critical size for irregularities in the surface is considered to be 0.1 \( \mu \)m (Buckton, 1990).

iii) Most of the compacts are required to be saturated, with the test liquid, before measurement. This can lead to swelling and deformation of the compact, producing a situation whereby the droplet is resting on a concentrated suspension rather than the powder surface (Buckton, 1990).

iv) The method is very dependant on the operator's technique, only experienced operators will produce consistent readings, since measurement depends on the ability to draw suitable tangents.

v) When drop height measurements are required errors may occur as a result of not being able to distinguish accurately the surface of the swollen powder disc.

vi) Dynamic effects of the contact angle make measurement with a protractor difficult. For example, the contact angle between the drop and the surface of paracetamol has been seen to reduce with time (Stamm et al, 1984) as a consequence of surface alteration to a state of lowest interfacial free energy by dissolution. This can be overcome to some extent by photographing the drop as soon as it is formed.
vii) The drop size must be controlled when using the direct measurement method. A drop size of 10 µl is recommended, as larger drops will be affected by gravitational forces (Buckton, 1990).

Although there are many criticisms of this technique, angles measured have been reported to be reproducible to within ± 4° (Lerk et al, 1977). Contact angles obtained by the h-e method have been noted to be lower than those measured by penetration methods (Luangtana-anan and Fell, 1988).

**Wilhelmy Gravitational Method**

This method is based on force measurements made when a compacted powder plate is immersed into a liquid. Powder plates are prepared using a stainless steel, highly polished, rectangular die of known dimensions. The plate is then suspended by a microbalance in the apparatus shown in figure 5.1. and makes contact with the test liquid, placed in a beaker below it, by means of a motorised stage. As the liquid and powder plate come into contact the changes in force acting upon the plate are recorded to produce a graphical output (fig. 5.2). Extrapolation of the second portion of the plot, representing the immersion of the plate, to the perpendicular line (x), drawn from the point of liquid/plate contact, gives the true force value, from which the contact angle is calculated (eqn. 5.6).

\[ \cos \theta = \frac{f g}{p \gamma_{lv}} \]

*Equation 5.6*

Where f=force, g=acceleration due to gravity, p=perimeter of the plate and \( \gamma_{lv} \)= interfacial tension between liquid and vapour.
Figure 5.1 Wilhelmy Apparatus (Schematic Diagram).

Figure 5.2 Typical Force as a function of Depth of Immersion Plot using Wilhelmy Gravitational Method
(Extrapolation of C-D back to perpendicular, A-B, gives true force (B-E)).
The Wilhelmy gravitational method has several advantages over other contact angle measurement techniques. The process is automated and therefore is not operator dependent. There is no need for pre-saturation of the powder compact with the test liquid and dynamic effects are avoided by instantaneous measurement. The plate is in contact with the vapour of the test liquid (the apparatus being enclosed) and if deformation of the plate occurs during measurement it will do so below the plate surface and therefore will not affect the results (Buckton, 1990). This method has the added advantage that contact angle hysteresis (changes in advancing and receding angle values) may be studied from the complete force profile plotted as a consequence of plate immersion and withdrawal during measurement. The main disadvantage of this method is the need to compress the test powders before measurement.

With all contact angle measurements, whether measured directly or indirectly, the powder surfaces may adsorb dirt, gas or vapour so altering the true angles (Odidi et al, 1991). Any method used should therefore, be consistent. Contact angle measurements using powder compacts are especially useful when considering interactions concerned with tableting (Buckton, 1988). It should be noted that contact angle measurements alone may be used for the assessment of wettability and/or dissolution and bioavailability (wettability is not necessarily an indication of dissolution, unless the solid is soluble in the liquid in question); liquid penetration into capillaries in capsules and tablets (although the significance of this has been questioned by Rowley and Newton, 1970); for optimisation of film coating techniques and drug release from matrixes (Singh et al, 1968). Alternative methods for assessing powder interfacial interactions include assessments based on the measurement of thermodynamic relationships between adsorption and immersion, immersion and adhesion, immersion and contact angle/surface tension and surface tension and immersion, using calorimetric methods, (reviewed by Buckton, 1988) and ultrasonic studies of particle assemblies (Kendall, 1991).
5.1.2 Calculation of Surface Energy

The first relationship between contact angle and surface energy was developed by Young (1805), where contact angle, $\theta$, was related to the equilibrium of the interfacial free energies between the solid-liquid ($\gamma_{sl}$) and the surface free energies of liquid ($\gamma_l$) and solid ($\gamma_s$) phases (eqn. 5.7)

$$\cos \theta = \frac{\gamma_s - \gamma_{sl} - \pi_e}{\gamma_l}$$  \hspace{1cm} \textit{Equation 5.7}

Where,

$$\pi_e = \gamma_s - \gamma_{sv}$$  \hspace{1cm} \textit{Equation 5.8}

Where, $\gamma_s$, $\gamma_l$, $\gamma_{sl}$, $\gamma_{sv}$, are the surface free energies of the solid, liquid and the interfacial free energies between solid-liquid and liquid-vapour respectively. $\pi_e$ is the spreading pressure and is described as the change in surface free energy, per square centimetre, due to any adsorption of vapour from the liquid to the solid surface. For systems where wetting is poor (contact angles larger than 10°) $\pi_e$ is zero, that is $\pi_e$ is negligible for relatively non polar solids at room temperature, when high boiling point solids are used. In these cases Young’s equation can be reduced to equation 5.9.

$$\cos \theta = \frac{\gamma_{sv} - \gamma_{sl}}{\gamma_{lv}}$$  \hspace{1cm} \textit{Equation 5.9}

Fox and Zisman (1950) developed an empirical method for determination of surface energy, based on Young’s equation, whereby the critical surface tension of a solid ($\gamma_c$) was defined as being equal to the highest surface tension of the liquid that would just spread over its surface. The method involved contact angle measurement using a homologous series of liquids. Extrapolation back to the intercept where $\cos \theta=1$, on a linear plot of $\cos \theta$ as a function of liquid surface tension, allowed the value critical
surface tension to be determined. This method was later shown to be improved in accuracy by plotting \( \cos \theta \) as a function of the square root of the liquid surface tension \( \gamma_{lv}^{-1/2} \).

Although \( \gamma_c \) gives an indication of the solid surface energy, the actual figure is given in terms of the interfacial energy between the solid and liquid and therefore does not represent the true surface energy. Subsequent to development, flaws in this technique have been noted (reviewed by Kloubek, 1992). The major criticisms were as follows; the method is very empirical, the value of \( \gamma_c \) obtained is dependent on the homologous series used, solutions of polar liquids yielded lower values (Dann, 1970), the relationship between \( \cos \theta \) and \( \gamma_{lv} \) was found to be not always linear (Dann, 1970) and problems in measurement occur when vapour is adsorbed or the solid surface is rough. Relationships between critical surface tension and surface energy have however, been deduced by Good and Girifalco (1960), who considered the critical surface tension \( \gamma_c \) to be equivalent to surface energy \( \gamma_s \), when systems are used in which the cohesive forces in both the liquids and the respective solid are of the same type as the adhesional forces (known as regular interfaces). The ratio between \( \gamma_c \) and \( \gamma_s \) depends on the interaction parameter, \( \Phi \) (eqn. 5.10).

\[
\gamma_s = \frac{\gamma_c}{\Phi^2} \quad \text{Equation 5.10}
\]

Where \( \Phi=1 \) for regular solids.

In summary, the critical surface tension method for surface energy evaluation is not recommended for its empirical nature and uncertainty about its physical meaning (Kloubek, 1992).

Numerous approaches for surface energy calculation have subsequently been developed (Kloubek, 1992). The most frequently used method however, is one based on the geometric mean theory developed by Fowkes (1964), who considered the
surface energy to be the summation of its interaction components (usually simplified to include only polar and dispersive components) and intermolecular attraction to occur exclusively between components of the same kind. This was later adapted by Wu (1973), who showed that the reciprocal mean approach provided better correlation between the experimental and theoretical results.

Surface energy is assumed to be the summation of its polar and dispersive components (eqn. 5.11)

\[ \gamma = \gamma^p + \gamma^d \]  \hspace{1cm} \textit{Equation 5.11}

Where \( \gamma^d \) represents the dispersive forces (London dispersive forces) and \( \gamma^p \) the polar interactions, due to all other forces, such as dipole interactions but predominately represents hydrogen bonding.

Wu (1973) has derived both the geometric and reciprocal (harmonic) mean approximate relationships, between work of adhesion between two phases and individual surface energies was presented. These relationships were derived from a knowledge of Fowkes’ work and manipulation of work of adhesion and cohesion equations expressed in molecular terms. A simplified outline of this is given below.

Work of adhesion between two phases \( (W_{a_{12}}) \) can be represented by equation 5.12

\[ W_{a_{12}} = \gamma_1 + \gamma_2 - \gamma_{12} \]  \hspace{1cm} \textit{Equation 5.12}

Resolving work of adhesion into its polar and dispersive components gives equation 5.13. Substitution of equation 5.12 into 5.13 gives equation 5.14 where work of adhesion is expressed in terms of surface energy

\[ W_{a_{12}} = W_{a_{12}}^p + W_{a_{12}}^d \]  \hspace{1cm} \textit{Equation 5.13}
\[ W_{a_{12}}^d + W_{a_{12}}^p = \gamma_1 + \gamma_2 - \gamma_{12} \quad \text{Equation 5.14} \]

Where \( \gamma_{12} \) is the interfacial tension between two phases, \( \gamma_1 \) and \( \gamma_2 \) are the individual surface tensions of each phase, \( W_{a_{12}}^p \) and \( W_{a_{12}}^d \) are the polar and nonpolar components of the work of adhesion.

Work of cohesion for the dispersive component (\( W_c^d \)) can be represented by equation 5.15.

\[ W_{c_1}^d = 2 \gamma_1^d \quad \text{Equation 5.15} \]

Manipulation of work of adhesion and cohesion equations expressed in terms of molecular properties led to derivation of two relationships between work of cohesion and adhesion (eqns. 5.16 and 5.17).

\[
W_{a_{12}}^d = \frac{2W_{c_1}^d W_{c_2}^d}{W_{c_1}^d + W_{c_2}^d} \quad \text{Equation 5.16}
\]

\[ W_{a_{12}}^d = 2(\gamma_1^d \gamma_2^d)^{0.5} \quad \text{Equation 5.17} \]

Combining equation 5.15 with equation 5.16 or equation 5.17 gives work of adhesion in terms of surface energy, expressed either as the reciprocal (harmonic) mean equation (eqn. 5.18) or the geometric mean (eqn. 5.19)
Chapter 5 - Surface Energetics

\[ W_{a_{12}}^d = \frac{4\gamma_1^d \gamma_2^d}{\gamma_1^d + \gamma_2^d} \quad \text{Equation 5.18} \]

\[ W_{a_{12}}^d = 2(\gamma_1^d \gamma_2^d)^{0.5} \quad \text{Equation 5.19} \]

The polar component of work of adhesion is more complicated because it represents more than one type of interaction. For simplicity all polar interactions were combined and considered as a single term, \( \gamma^p \), giving the harmonic mean equation 5.20 and the geometric mean equation 5.21. It was found however that most cases could be represented by the harmonic mean equation (Wu, 1973) (eqn. 5.20).

\[ W_{a_{12}}^p = \frac{4\gamma_1^p \gamma_2^p}{\gamma_1^p + \gamma_2^p} \quad \text{Equation 5.20} \]

\[ W_{a_{12}}^p = 2(\gamma_1^p + \gamma_2^p)^{0.5} \quad \text{Equation 5.21} \]

Combination of equations 5.14 with equations 5.18 and 5.20 gives the harmonic mean equation for the interfacial energy between two phases (eqn. 5.22). Which is the preferred equation for use with low energy systems, such as, water, organic liquids and polymers. Similarly combination of equations 5.14, 5.19 and 5.21 gives the geometric mean equation for interfacial free energy between two phases (eqn. 5.23).

\[ \gamma_{12} = \gamma_1 + \gamma_2 - 4\left[ \frac{\gamma_1^d \gamma_2^d}{\gamma_1^d + \gamma_2^d} - \frac{\gamma_1^p \gamma_2^p}{\gamma_1^p + \gamma_2^p} \right] \quad \text{Equation 5.22} \]
Chapter 5 - Surface Energetics

\[ \gamma_{12} = \gamma_1 + \gamma_2 - 2[(\gamma_1^d \gamma_2^d)^{0.5} + (\gamma_1^p \gamma_2^p)^{0.5}] \quad \text{Equation 5.23} \]

Combination of Young's equation (eqn. 5.9) and the harmonic mean equation (eqn. 5.22) or the geometric mean equation (eqn. 5.23) gives equations 5.24 and 5.25, whereby a relationship between contact angle (between liquid and solid) and surface energy is established (Zografi and Tam, 1976).

\[ (b+c-a)\gamma_s^d \gamma_s^p + c(b-a)\gamma_s^d + b(c-a)\gamma_s^p - abc \quad \text{Equation 5.24} \]

\[ \gamma_1 (1+\cos \theta) = 2[(\gamma_1^d \gamma_2^d)^{0.5} + (\gamma_1^p \gamma_2^p)^{0.5}] \quad \text{Equation 5.25} \]

Where \( a=(\gamma_s^4/4)(1+\cos \theta) \), \( b=\gamma_s^d \) and \( c=\gamma_s^p \)

Even if the surface energy and its components are known for one phase, two unknown parameters, \( \gamma_2^p \) and \( \gamma_2^d \) exist. In order to obtain the polar and dispersive component surface energies for the solid phase contact angle measurements must be made using two liquids of known polar (\( \gamma_s^p \)) and dispersive (\( \gamma_s^p \)) components and the equations solved simultaneously to find the bit fit for the data, using computer analysis.

It should be noted that although this method is commonly used for surface energy determination and is the method employed in this research, the theoretical validity has been questioned in favour of an alternative method, the equation of state approach. The equation of state approach (Neumann et al, 1974), based on thermodynamic arguments, concludes that the solid-liquid surface tension is dependent only on the total solid and liquid surface tensions rather than their individual components. Spelt et al (1986) showed, experimentally, that contact angle measurements were found to
be similar, when their surface tensions were of equal magnitude regardless of the magnitude of their dispersive components.

5.1.3 Calculation of Other Parameters

Using Surface Energy Relationships

The use of surface free energy calculation lies in its application in calculation of other parameters, such as polarity, work of cohesion, work of adhesion and spreading coefficients. All of which permit predictions of material behaviour and interaction with other phases.

Polarity

The polarity of a phase \( \chi^p \) is expressed as the ratio of its polar component to the total surface energy (eqn. 5.26) (Wu, 1973).

\[
\chi^p = \frac{\gamma^p}{\gamma}
\]

*Equation 5.26*

Similarly, percentage polarity can be calculated.

Works of Cohesion, Adhesion and Spreading Coefficient

As described earlier the work of adhesion (eqn. 5.28 or eqn. 5.29) and cohesion (eqn. 5.27) can be calculated from a knowledge of surface energy and polarity (Wu, 1973).

\[
W_c = 2(\gamma^p + \gamma^d)
\]

*Equation 5.27*

\[
W_a = 4\left(\frac{\gamma^d_1 \cdot \gamma^d_2}{\gamma^d_1 + \gamma^d_2} + \frac{\gamma^p_1 \cdot \gamma^p_2}{\gamma^p_1 + \gamma^p_2}\right)
\]

*Equation 5.28*
Chapter 5 - Surface Energetics

\[ W_e = 2(\gamma_1^d - \gamma_2^d)^{0.5} + 2(\gamma_1^p - \gamma_2^p)^{0.5} \quad \text{Equation 5.29} \]

Wu (1973) showed that the optimum wettability could be described by the spreading coefficient, \( \lambda_{12} \), of one phase on another (eqn. 5.30).

\[ \lambda_{12} = \gamma_1 - \gamma_2 - \gamma_{12} \quad \text{Equation 5.30} \]

Substitution of equation 5.22 into equation 5.30 gives equation 5.31, which by comparing to equations 5.27 and 5.28 could be represented by the difference between in works of adhesion and cohesion.

\[ \lambda_{12} = 4(\frac{\gamma_1^d \cdot \gamma_2^d}{\gamma_1^d + \gamma_2^d} + \frac{\gamma_1^p \cdot \gamma_2^p}{\gamma_1^p + \gamma_2^p} - \frac{\gamma_1}{2}) \quad \text{Equation 5.31} \]

The spreading coefficient, that is the degree to which one phase will spread over another, is particularly useful in prediction of interactions between phases and has not only been used by Wu (1973) for optimum wettability determination but also for prediction of stability of non aqueous, non polar suspensions (Parsons et al, 1992).

In this research the above relationships have been used for powder systems, the aim being to use surface energy and polarity to predict powder behaviour in dry powder aerosol formulation. By calculation of the works of adhesion, cohesion and the spreading coefficient between the drug and its inert carrier material it may be possible the in vivo behaviour of a drug.
5.2 Materials and Methods

5.2.1 Materials

Salbutamol Sulphate, Micronised.
Micro Macinazone SA, Microgrinding Ltd., Switzerland.

Salbutamol Sulphate, Spray Dried.
Prepared by Spray Drying.

Lactose Medium Grade.
Batch No. 2862
Lactocham, Slatney, Cheshire, UK.

Lactose, Spray Dried.
BP/EP DC L11
DMV.

Bromonaphthalene.
SI N. 2810
FSA Laboratory Supplies, Loughborough, UK.

Cyclohexane, HPLC grade.
Aldrich Chemical Co. Inc., Milwauke, USA.

Ethylene Glycol, spectrophotometric grade.
Aldrich Chemical Co. Inc., Milwauke, USA.

Formamide.
Lot 32H0899
Sigma Chemical Co., St. Louis, USA.
5.2.2 Methods

Contact Angle Measurement

Contact angles were measured using the Wilhelmy technique (section 5.1.1). The powder compacts were prepared using a highly polished, stainless steel, rectangular die (fig. 5.3). A known weight of powder was placed into the die, which was subsequently placed under pressure for a set period of time, 5 minutes. The resulting powder compact was then gently removed from the die. Contact with the die surface was avoided in order to minimise any adsorption of grease from the skin onto the compact surface. Once prepared the thickness and end width of the compact was measured using a set of digital callipers and the perimeter calculated (it was assumed that the plate was of uniform thickness throughout its length). Several plates were prepared together and stored in a desiccator, containing silica gel (RH 0%) until required for contact angle measurement, at which time they were equilibrated in air.
The powder compacts were suspended on an electro-microbalance, in the dynamic contact angle analyser (DCA, System 312, Cahn Instruments Inc., Cerritos, USA) by means of a metal clip and wire. The test liquid was poured into a thoroughly cleaned, glass beaker placed in a controlled temperature water bath, positioned on the motorised stage below the powder compact. The powder compact was then allowed to come into contact with the liquid by the raising of the motorised stage at a pre-set, the speed of which had been pre-set (approximately 200 μm sec⁻¹).
The compacts were allowed to be imnersed to a depth of 5 mm before the stage was lowered to its original position. During this procedure, changes in the force acting on the plate were recorded to produce a force-immersion profile. Portions of this profile (methylene iodide) against the spray dried and micronised salbutamol sulphate powder compacts. In each case measurements were repeated five or more times and the average Cos θ calculated. The surface free polar and dispersive energies for each liquid were obtained from the literature (table 5.1). The validity of these values were confirmed by the results of the above investigations, the effect of pressure, during powder compaction, on the contact angle and consequently the surface energy was investigated using spray dried salbutamol sulphate. Spray dried salbutamol sulphate was chosen after it was noted that pressures above 1 ton (1 ton = 1016.05 Kg) produced opaque powder compacts, implying that some sort of powder deformation may have occurred. Compacts were made using 250 mg of powder, held at pressures of 1, 2 or 3 tons for five minutes. A sample of each plate type was viewed for surface detail using scanning electron microscopy (Phillips XL20).
Chapter 5 - Surface Energetics

The compacts were allowed to be immersed to a depth of 5 mm before the stage was lowered to its original position. During this procedure changes in the force acting on the plate were recorded to produce a force-immersion profile. Portions of this profile were then selected, for advancing and receding angle calculation performed by the computer (eqn. 5.6).

In order to compare two or more powders the experimental conditions used were standardised. Preliminary work on the powder compact production was performed in order to determine the best experimental conditions. Pressures between 1 and 5 tonnes, powder weights of between 150-250 mg and storage conditions were examined for micronised and spray dried salbutamol sulphate.

Two test liquids of known polar and dispersive components are required for the surface energy calculation. The liquids must be as different in polarity as possible, they should not dissolve the powder under investigation and should produce advancing angles greater than zero (that is Cos θ ≤ 1). Several liquids were tested; cyclohexane, bromonaphthalene, water, ethylene glycol, glycerol, formamide and diiodomethane (methylene iodide) against the spray dried and micronised salbutamol sulphate powder compacts. In each case measurements were repeated five or more times and the average Cos θ calculated. The surface free polar and dispersive energies for each liquid were obtained from the literature (table 5.1). The validity of these values were confirmed by a single measurement made using a glass slide prior to use.

In addition to the above investigations the effect of pressure, during powder compaction, on the contact angle and consequently the surface energy was investigated using spray dried salbutamol sulphate. Spray dried salbutamol sulphate was chosen after it was noted that pressures above 1 ton (1 ton = 1016.05 Kg) produced opaque powder compacts, implying that some sort of powder deformation may have occurred. Compacts were made using 250 mg of powder, held at pressures or 1, 2 or 3 tons for five minutes. A sample of each plate type was viewed for surface detail using scanning electron microscopy (Phillips XL20).
Chapter 5 - Surface Energetics

### Table 5.1 Literature Surface Energies (mN m⁻¹) for Test Liquids used in Contact Angle Measurement

<table>
<thead>
<tr>
<th>Sample</th>
<th>(\gamma_v)</th>
<th>(\gamma_p)</th>
<th>(\gamma_d)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bromonaphthalene</td>
<td>44.0</td>
<td>-</td>
<td>44.0</td>
<td>Van Oss et al (1992)</td>
</tr>
<tr>
<td>Cyclohexane</td>
<td>27.8</td>
<td>0.9</td>
<td>26.9</td>
<td>Luangtana-Anan and Fell (1988)</td>
</tr>
<tr>
<td>Ethylene Glycol</td>
<td>48.9</td>
<td>15.5</td>
<td>33.3</td>
<td>Zografi and Tam (1976)</td>
</tr>
<tr>
<td>Formamide</td>
<td>58.0</td>
<td>19.0</td>
<td>39.0</td>
<td>Van Oss et al (1992)</td>
</tr>
<tr>
<td>Glycerol</td>
<td>63.3</td>
<td>26.4</td>
<td>37.0</td>
<td>Wright (1983)</td>
</tr>
<tr>
<td>Propylene Glycol</td>
<td>38</td>
<td>9.4</td>
<td>28.6</td>
<td>In house data</td>
</tr>
<tr>
<td>Water</td>
<td>72.0</td>
<td>48.8</td>
<td>23.2</td>
<td>Zografi and Tam (1976)</td>
</tr>
<tr>
<td>Diiodomethane</td>
<td>50.4</td>
<td>0.0</td>
<td>50.4</td>
<td>Zografi and Tam (1976)</td>
</tr>
</tbody>
</table>

5.3 Results and Discussion

5.3.1 Contact Angle Measurements

Contact angles measured using the test liquids are presented in table 5.2 for spray dried salbutamol sulphate and in table 5.3 for the micronised salbutamol sulphate. The contact angles measured using test liquids other than those presented in table 5.2 and 5.3 were undefined (Cos \(\theta\) ≥1) and were therefore, rejected as being unsuitable for contact angle measurement.
### Table 5.2 Contact Angle Measurements (advancing angle) using Spray Dried Salbutamol Sulphate.

<table>
<thead>
<tr>
<th>Liquid</th>
<th>Pressure (ton)</th>
<th>Weight (mg)</th>
<th>n</th>
<th>Contact Angle ± S.D.</th>
<th>Cos θ ± S.D.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethylene Glycol</td>
<td>1</td>
<td>150</td>
<td>7</td>
<td>40.62° ± 11.87°</td>
<td>0.75 ± 0.13</td>
</tr>
<tr>
<td>Bromonaphthalene</td>
<td>1</td>
<td>150</td>
<td>8</td>
<td>26.73° ± 16.71</td>
<td>0.86 ± 0.14</td>
</tr>
<tr>
<td>Formamide</td>
<td>1</td>
<td>250</td>
<td>5</td>
<td>35.13° ± 8.32°</td>
<td>0.81 ± 0.087</td>
</tr>
<tr>
<td>Glycerol</td>
<td>1</td>
<td>250</td>
<td>6</td>
<td>66.60° ± 12.38°</td>
<td>0.39 ± 0.19</td>
</tr>
</tbody>
</table>

### Table 5.3 Contact Angle (advancing angle) Measurements using Micronised Salbutamol Sulphate.

<table>
<thead>
<tr>
<th>Liquid</th>
<th>Pressure (ton)</th>
<th>Weight (mg)</th>
<th>n</th>
<th>Contact Angle ± S.D.</th>
<th>Cos θ ± S.D.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethylene Glycol</td>
<td>1</td>
<td>150</td>
<td>12</td>
<td>15.35° ± 3.49°</td>
<td>0.96 ± 0.02</td>
</tr>
<tr>
<td>Ethylene Glycol</td>
<td>5</td>
<td>150</td>
<td>7</td>
<td>27.28° ± 2.89°</td>
<td>0.89 ± 0.02</td>
</tr>
<tr>
<td>Formamide</td>
<td>1</td>
<td>250</td>
<td>10</td>
<td>12.47° ± 3.09°</td>
<td>0.98 ± 0.01</td>
</tr>
<tr>
<td>Glycerol</td>
<td>1</td>
<td>250</td>
<td>9</td>
<td>56.27° ± 6.63°</td>
<td>0.56 ± 0.10</td>
</tr>
<tr>
<td>Bromonaphthalene</td>
<td>5</td>
<td>150</td>
<td>10</td>
<td>22.31° ± 4.23°</td>
<td>0.92 ± 0.03</td>
</tr>
</tbody>
</table>
Spray dried salbutamol sulphate produced opaque, yellowish compacts when preparation pressures of greater than 1 ton were employed. The scanning electron micrographs showed that at pressures of 1 ton (plate 5.1) the surface was not smooth and continuous, but existed as individual, spherical particles (comparison with plate 2.6 show these to be similar to the non compressed material). As the pressure was increased the compact surface became smoother and the particles appeared crushed (plate 5.2). At pressures of three tons (plate 5.3) and greater the surface was completely smooth. The surface roughness seen when preparation pressures of 1 ton were employed potentially could have had two consequences; the first being increased hysteresis between advancing and receding angles and secondly error in contact angle measurement. Surface roughness and its effect on contact angle, mainly hysteresis between advancing and receding angle has been noted previously (Zografi and Johnson, 1984). Errors in contact angle measurement could be caused by incorrect compact perimeter estimation. Simple length and breath measurements will not have accounted for the increased surface caused by spherical particles lying along the compact surface, this in turn will have affected the contact angle measurement based on equation 5.6. Although this problem could have been eliminated by increase in compact production pressure, the change in surface leads to the question of whether

<table>
<thead>
<tr>
<th></th>
<th>Propylene Glycol</th>
<th>Glycerol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Contact Angle ±</td>
<td>Cos θ ± S.D.</td>
</tr>
<tr>
<td></td>
<td>S.D</td>
<td></td>
</tr>
<tr>
<td>Spray Dried Lactose</td>
<td>18.31° ± 6.42°</td>
<td>0.94 ± 0.04</td>
</tr>
<tr>
<td>Medium Grade Lactose</td>
<td>13.50° ± 5.91°</td>
<td>0.97 ± 0.03</td>
</tr>
</tbody>
</table>

*Table 5.4 Contact Angle Measurements (advancing angle) for Spray Dried and Medium Grade Lactose using Propylene Glycol and Glycerol Test Liquids.*
the subsequent contact angle measurements and hence surface energy would be truly representative of the non compacted powder. For this reason low pressures (1 ton) were used for comparison between micronised and spray dried salbutamol sulphate.

In a study by Kiesvaara (1991), it was shown that changes in compact preparation pressure usually resulted in changes in the measured polar component of surface energy, which was thought to be caused by changes in electronegativity at the surface. It was also noted that compression, by altering the actual surface area covered by the liquid, may be responsible for change in measured contact angles and hence surface energy. Micronised salbutamol sulphate produced smooth compacts at all pressures used.

5.3.2 Calculation of Surface Energy

Surface energy calculations were determined by computer analysis using both the harmonic (reciprocal) mean equation (eqn. 5.22) and the geometric mean equation (eqn. 5.23). Surface energy calculations were performed using contact angle measurements from several test liquids are presented in table 5.5 for the spray dried salbutamol sulphate and in table 5.6 for the micronised salbutamol sulphate.
Plate 5.1  Surface of Spray Dried Salbutamol Sulphate Compact
Prepared using 1 Ton Pressure.

Plate 5.2  Surface of Spray Dried Salbutamol Sulphate Compact
Prepared using 2 Tons Pressure.

Plate 5.3  Surface of Spray Dried Salbutamol Sulphate Compact
Prepared using 3 Tons Pressure.
Chapter 5 - Surface Energetics

<table>
<thead>
<tr>
<th>Liquid I</th>
<th>Liquid II</th>
<th>Calculated using Harmonic Mean</th>
<th>Calculated using Geometric Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>$\gamma_s$</td>
<td>$\gamma_f$</td>
</tr>
<tr>
<td>Ethylene Glycol</td>
<td>Bromonaphthalene</td>
<td>42.87</td>
<td>38.24</td>
</tr>
<tr>
<td>Ethylene Glycol</td>
<td>Formamide</td>
<td>-114.49</td>
<td>3.99</td>
</tr>
<tr>
<td>Bromonaphthalene</td>
<td>Formamide</td>
<td>49.17</td>
<td>39.42</td>
</tr>
<tr>
<td>Ethylene Glycol</td>
<td>Glycerol</td>
<td>(Cannot be solved)</td>
<td>792.75</td>
</tr>
<tr>
<td>Glycerol</td>
<td>Bromonaphthalene</td>
<td>41.87</td>
<td>38.24</td>
</tr>
<tr>
<td>Glycerol</td>
<td>Formamide</td>
<td>Cannot be solved</td>
<td>245.15</td>
</tr>
</tbody>
</table>

Table 5.5 Calculated Surface Energies (mN m$^{-1}$) for Spray Dried Salbutamol Sulphate.

Theoretically it should not matter which two liquids are used for contact angle measurement, the final calculated surface energy should be the same. Spelt et al (1986) have shown pairs of liquids of equal surface tension to yield contact angles of equal magnitude. Tables 5.5 and 5.6 show that this is clearly not the case in this instance. Therefore it would be sensible when comparing two or more powders to use contact angle data measured using the same pair of test liquids for both powders. The test liquids chosen should be as different in surface tension and polarity as possible. In this case however, liquids with low surface tensions were found to produce undefined angles with both spray dried and micronised salbutamol sulphate. Finding suitable test liquids, with adequate reproducibility was difficult.


Chapter 5 - Surface Energetics

<table>
<thead>
<tr>
<th>Liquid I</th>
<th>Liquid II</th>
<th>Calculated using Harmonic Mean</th>
<th>Calculated using Geometric Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>$\gamma_s$</td>
<td>$\gamma^f$</td>
</tr>
<tr>
<td>Ethylene Glycol</td>
<td>Formamide</td>
<td>-131.11</td>
<td>8.10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Cannot be solved)</td>
<td></td>
</tr>
<tr>
<td>Ethylene Glycol</td>
<td>Glycerol</td>
<td>Cannot be solved</td>
<td></td>
</tr>
<tr>
<td>Formamide</td>
<td>Glycerol</td>
<td>Cannot be solved</td>
<td></td>
</tr>
<tr>
<td>Ethylene Glycol*</td>
<td>Bromonaphthalene*</td>
<td>47.52</td>
<td>40.62</td>
</tr>
</tbody>
</table>

Table 5.6 Calculated Surface Energies (mN m$^{-1}$) for Micronised Salbutamol Sulphate.

(* data using compacts prepared with 5 tons pressure.)

As mentioned above it would be expected that two liquids of similar surface tension and polarity would yield similar contact angles with the same powder. This was not the case with formamide and glycerol (tables 5.2 and 5.3) and is the most probable reason for the inability of the computer to solve the simultaneous harmonic mean equation using this data. It was however, possible to obtain surface energy values for spray dried and micronised salbutamol sulphate, with the contact angle data for formamide and glycerol test liquids using the geometric mean equation. These values greatly exceeded the expected surface energy values. Surface energies for many pharmaceutical powders have been measured and were reported to lie between 38.6 and 94.4 mN m$^{-1}$ (Lerk et al, 1977). The values obtained here are more in the order that would be expected for metal materials.

One explanation for the differences in contact angle measurements obtained using formamide, ethylene glycol and glycerol (all of which have similar surface tensions) could be that there is an interaction between these liquids and the powder surface. Glycerol, formamide and ethylene glycol are all semi-polar molecules and therefore,
some molecular orientation may be occurring at the powder surface. This problem can sometimes be overcome by the use of a more symmetrical molecule such as diiodomethane (methylene iodide) or water (Zografi and Tam, 1976), however, both these liquids spread over the salbutamol sulphate powders (thus giving undefined contact angles).

From table 5.5 it would seem that the most reasonable surface energy values for spray dried salbutamol sulphate powder are those calculated from contact angle measurements made with the following liquid pairs; ethylene glycol and bromonaphthalene, bromonaphthalene and formamide and glycerol and bromonaphthalene. In these three cases the calculated surface energy values using the harmonic or geometric mean agree, suggesting that the data fits closely to the derived surface energy equations. However, with liquid pairs ethylene glycol and bromonaphthalene and glycerol and bromonaphthalene the polar components were unusually low (especially when the structure is considered, Appendix 2). The most reasonable surface energy value would therefore, appear to be that given by contact angle measurements made with bromonaphthalene and formamide. Differences in the polar component caused by using two different equations (the harmonic and geometric mean) has been noted (Parsons et al, in press). It was shown that systems which produced consistent results, (especially when using diiodomethane as one of the test liquids) when computed using both the geometric and harmonic mean equations gave different polar component values. The reason for this was thought to be due to the differences in the mean used. Only liquids with values for polar and dispersive components equal to that of the solid’s components would yield the same values using either equation. It was suggested that a way of reducing this effect would be, if possible, to chose dispersive (diiodomethane) and polar (water) test liquids as the to test liquids for contact angle measurements, to ensure that both the polar and dispersive components of the solid were fully compensated for when calculating surface energy.
Using similar arguments, the most likely surface energy value for micronised salbutamol sulphate, from table 5.6, would appear to be that given by contact angle measurements using the liquid pair, ethylene glycol and bromonaphthalene.

From the contact angle measurements presented in table 5.4, the surface energies for spray dried and medium grade lactose were calculated, using both the geometric and harmonic mean equations (table 5.7).

<table>
<thead>
<tr>
<th></th>
<th>Calculated using Harmonic Mean</th>
<th>Calculated using Geometric Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\gamma_s$</td>
<td>$\gamma^d$</td>
</tr>
<tr>
<td>Spray Dried Lactose</td>
<td>87.02</td>
<td>15.67</td>
</tr>
<tr>
<td>Medium Grade Lactose</td>
<td>73.56</td>
<td>16.98</td>
</tr>
</tbody>
</table>

Table 5.7 Calculated Surface Energies (mN m$^{-1}$) for Spray Dried and Medium Grade Lactose.

The results show that there are many limitations to the technique used for surface energy calculations. It was shown that changes in experimental procedure such as quantity of powder and pressure used for powder compact production and the test liquid pair used can greatly affect the final result. Much of the problem lies with the salbutamol powders themselves. Previous work in this area has shown that when two liquids, which are sufficiently different in polarity, can be used for contact angle measurements which are reproducible then reliable surface energy results can be obtained.
5.3.3 Calculation of Work of Cohesion, Work of Adhesion and Spreading Coefficients

In order to investigate the potential use of surface energy and polarity in dry powder aerosol formulation the surface energy for spray dried salbutamol sulphate, calculated from contact angle measurements using bromonaphthalene and formamide, and for micronised salbutamol, calculated from contact angle measurements using ethylene glycol and bromonaphthalene, were selected as the most reasonable values based on the arguments discussed above (table 5.8). These, together with surface energies for spray dried and medium grade lactose (table 5.8) were used to calculate work of adhesion and spreading coefficients.

<table>
<thead>
<tr>
<th></th>
<th>$\gamma_s$</th>
<th>$\gamma^f$</th>
<th>$\gamma^p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spray Dried Salbutamol Sulpha.</td>
<td>49.17</td>
<td>38.24</td>
<td>10.92</td>
</tr>
<tr>
<td>Micronised Salbutamol Sulpha.</td>
<td>47.52</td>
<td>40.62</td>
<td>6.90</td>
</tr>
<tr>
<td>Medium Grade Lactose</td>
<td>73.56</td>
<td>16.98</td>
<td>56.57</td>
</tr>
<tr>
<td>Spray Dried Lactose</td>
<td>87.02</td>
<td>15.67</td>
<td>71.35</td>
</tr>
</tbody>
</table>

Table 5.8 Surface Energies and Components (mN m$^{-1}$) used to Calculate Work of Cohesion, Work of Adhesion and Spreading Coefficients.

Works of cohesion were calculated using equation 5.27 and are presented in table 5.9. Works of adhesion between salbutamol sulphate and lactose were calculated using equation 5.28, where phase I, was considered to be either spray dried of micronised salbutamol sulphate and phase II, either the medium grade or spray dried lactose (table 5.10).
Chapter 5 - Surface Energetics

<table>
<thead>
<tr>
<th>Material</th>
<th>Work of Cohesion ((W_J) \text{ mN m}^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spray Dried Salbutamol Sulphate</td>
<td>98.34</td>
</tr>
<tr>
<td>Micronised Salbutamol Sulphate</td>
<td>95.04</td>
</tr>
<tr>
<td>Medium Grade Lactose</td>
<td>147.12</td>
</tr>
<tr>
<td>Spray Dried Lactose</td>
<td>174.04</td>
</tr>
</tbody>
</table>

*Table 5.9 Calculated Works of Cohesion.*

<table>
<thead>
<tr>
<th>Phase I</th>
<th>Phase II</th>
<th>Work of Adhesion ((W_J) \text{ mN m}^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spray dried Salbutamol Sulphate</td>
<td>Medium Grade Lactose</td>
<td>83.65</td>
</tr>
<tr>
<td>Spray Dried Salbutamol Sulphate</td>
<td>Spray Dried Lactose</td>
<td>82.34</td>
</tr>
<tr>
<td>Micronised Salbutamol Sulphate</td>
<td>Medium Grade Lactose</td>
<td>72.53</td>
</tr>
<tr>
<td>Micronised Salbutamol Sulphate</td>
<td>Spray Dried Lactose</td>
<td>70.43</td>
</tr>
</tbody>
</table>

*Table 5.10 Works of Adhesion between Salbutamol Sulphate and Lactose Powders.*

The spreading coefficients of salbutamol sulphate (spray dried or micronised) over lactose (medium grade or spray dried) and vice versa were calculated using equation 5.31 (table 5.11).

Work of cohesion, work of adhesion and spreading coefficients may be useful in the evaluation of dry powders for dry powder aerosol delivery. For example, work of cohesion (table 5.9) is greater for spray dried salbutamol sulphate than for the micronised salbutamol sulphate. This is reflected by experimental work presented in
Chapter 4. The flowability and cohesive indices for spray dried salbutamol sulphate were lower than that of the micronised material (table 4.11), indicating higher cohesive forces and poorer flow. In vitro deposition studies, using the twin impinger, demonstrated higher percentage deposition in stage II for micronised sulphate than spray dried salbutamol sulphate, when liberated from either Rotahaler® or the Spinhaler® (tables 4.14 and 4.15). Deposition in stage II of the twin impinger depends, to a certain extent, on the ability of the drug to deaggregate when liberated into the air stream from the device. The higher cohesive forces between particles of spray dried salbutamol sulphate may have lead to aggregate deposition as opposed to particle deposition and hence may be the reason for lower stage II percentage deposition.

Works of adhesion between spray dried or micronised salbutamol sulphate and spray dried or medium grade lactose (table 5.10) do not relate well to twin impinger analysis for capsules containing drug and carrier (table 4.16). However, the work of adhesion between the powders and the gelatin of the capsule, which is unknown, may be the preferred reaction in the case of low stage II deposition.

A positive spreading coefficient values indicate spreading is favoured. In table 5.10 all spreading coefficients are negative indicating the spreading is not favoured. In the case of drug and carrier preparations therefore, the work of cohesion is probably the a more important in the evaluation of in vitro deposition.

It should be noted that although surface energy, polarity and works of cohesion have been shown to correspond to properties of flow and in vitro deposition using twin impinger analysis, the surface energies selected were used as in this example.
<table>
<thead>
<tr>
<th>Phase I</th>
<th>Phase II</th>
<th>Spreading Coefficient $(\lambda_{12})$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spray Dried Salbutamol Sulphate</td>
<td>Medium Grade Lactose</td>
<td>-14.69</td>
</tr>
<tr>
<td>Medium Grade Lactose</td>
<td>Spray Dried Salbutamol Sulphate</td>
<td>-63.47</td>
</tr>
<tr>
<td>Spray Dried Salbutamol Sulphate</td>
<td>Spray Dried Lactose</td>
<td>-16.0</td>
</tr>
<tr>
<td>Spray Dried Lactose</td>
<td>Spray Dried Salbutamol Sulphate</td>
<td>-91.70</td>
</tr>
<tr>
<td>Micronised Salbutamol Sulphate</td>
<td>Medium Grade Lactose</td>
<td>-22.51</td>
</tr>
<tr>
<td>Medium Grade Lactose</td>
<td>Micronised Salbutamol Sulphate</td>
<td>-144.59</td>
</tr>
<tr>
<td>Micronised Salbutamol Sulphate</td>
<td>Spray Dried Lactose</td>
<td>-24.61</td>
</tr>
<tr>
<td>Spray Dried Lactose</td>
<td>Micronised Salbutamol Sulphate</td>
<td>-103.61</td>
</tr>
</tbody>
</table>

\textit{Table 5.11 Spreading Coefficients $(\lambda_{12}$ and $\lambda_{21}$) for Salbutamol Sulphate and Lactose Powders.}

Low energy powders would need to be tested using this method for a true evaluation of the suitability of surface energy and polarity for use in dry powder aerosol formulation.
5.4 Conclusions

Preliminary work in the use of contact angle measurement to calculate surface energy and polarity, for subsequent calculation of works of adhesion, cohesion and spreading coefficients, has been shown to have potential in the prediction of in vitro behaviour of powders to be used in dry powder aerosol formulation.

There are many potential sources of error associated with the technique. The use of powder compacts may lead to errors in bulk powder surface energy. Experimental work showed the importance of choice of conditions used for contact angle measurement. Quantity of powder used in preparation of compact and the pair of test liquids used to evaluate surface energy was shown to be important. The degree of compression of spray dried salbutamol was seen to affect the roughness of powder compact produced, pressures of above 1 ton caused deformation. Because of the many potential sources of error associated with this technique, for high energy materials, it more likely that its potential will be qualitative rather than quantitative.
Chapter Six

Summary and Further Work
Summary

6.1 Summary

The aim of this research was to produce drug powders suitable for therapeutic dry powder aerosol formulation. Dry powder aerosols are important alternatives to metered dose inhalers and have the advantages of being breath actuated, they do not contain propellants or any other harmful excipients and are potentially easier to manufacture. As is the case with all drug delivery to the lung the major formulation difficulty lies in achieving the correct particle size. An ideal drug powder to be used in dry powder aerosol formulation would be one where the drug is presented in the respirable size range (≤ 10 μm, Gonda and Byron, 1978), is not adhesive, cohesive or static in nature, flows well into and out of its liberation device, preferably without a carrier but deaggregates efficiently when mixed with a carrier. The powder should also be stable in most atmospheric conditions.

The most important property of a drug to be delivered to the lung besides its pharmacological activity is that of size. It has been shown that most particles depositing in the upper airways will be removed by the lungs mucociliary action. Therefore, to achieve an effective therapeutic effect a drug should be deposited in the lower lung. Drug powders are most commonly reduced in size by micronisation, a milling method, usually a fluid jet type is employed. In this research spray drying was investigated as a suitable alternative means of controlled particle size reduction. Previous work using spray drying in radio labelling techniques for lung deposition studies of sodium cromoglycate, indicated that this technique was potentially applicable (Vidgren et al, 1987b). Spray drying is a process whereby a solution, slurry or suspension is atomised into fine spray, mixed with warm air and allowed to evaporate to a dry particulate powder. It has the advantage of being a simple one stage process, suitable for thermolabile materials and has been exploited by many industries including the pharmaceutical industry, to produce products of well defined physical and chemical properties. The spray dryer type and design are important for the final production.
product produced. In this research a Büchi 190 mini spray dryer was employed and all materials were spray dried from aqueous solutions.

Initially the drugs: isoprenaline, hydrochloride and sulphate; salbutamol base and sulphate and pentamidine isethionate were spray dried to test the suitability of the technique and to select a suitable model drug on which to perform further studies. It was found that although the spray drying process could be manipulated to produce spherical particles (viewed using scanning electron microscopy) in the respirable size range (sized by laser diffraction), for all the drugs investigated with the exception of isoprenaline hydrochloride and pentamidine isethionate. Optimisation of the process in terms of particle size and percentage yield proved difficult. Changing one factor at a time was not only time consuming because of the number of variables, but also did not take into consideration any interdependence between factors. The use of a factorial design analysis proved to be a more suitable means for optimisation of the spray drying process, it not only allowed investigation of a number of factors over a range of conditions but also indicated any interactive effects occurring between variables. A $2^4$ factorial design was chosen to investigate the effect of pump speed, aspirator level (the rate at which air is pulled through the spray dryer), heat control level and feed concentration on particle size and percentage yield of salbutamol sulphate. Salbutamol sulphate was chosen from the preliminary work because of the ease with which it spray dried, its solubility and fame, availability and the availability with which prepared formulations could be compared. It was discovered that for median particle size no one factor alone was important but the interaction between the feed concentration and the aspirator level were important. An increase in both these factors lead to an increase in median particle size. Percentage yield was found to be influenced by changes in aspirator level, feed concentration and the interaction between pump rate and feed concentration.

From a knowledge of the spray drying process, gained from both preliminary findings and factorial design analysis, further experiments were performed using spray dried salbutamol sulphate spray dried under the following conditions: feed concentration, 10% w/v; pump rate, 7 ml min$^{-1}$, air flow rate, 800 NI h$^{-1}$; aspirator level, 18; inlet
temperature, 151-153 °C and outlet temperature, 80-85 °C. The chemical, physical and aerodynamic properties of the spray dried salbutamol sulphate were investigated and compared to those of micronised drug.

Spray drying salbutamol sulphate produced spherical, often pitted particles (viewed using scanning electron microscopy), with a mean (number) particle size of 1.6 μm (measured by computer image analysis of the S.E.M. micrograph), median particle size of 4.78 μm measured by laser diffraction and a MMAD 5.27 μm (calculated from density and median particle size). Spray drying was not seen to destroy the potency of the salbutamol sulphate (measured using fluorometry) although it was reduced slightly (95% activity of the micronised material), nor change it chemically (shown by infra red spectroscopy). The crystallinity and the differential scanning calorimetric thermograms were however, seen to be altered. Spray drying caused the salbutamol sulphate to become less crystalline (shown by X-ray diffraction). The apparent density (measured using an air comparison pycnometer) of the spray dried salbutamol was seen to be less than that of the micronised. The bulk density and compressibility (Carr's compressibility ratio) were seen to increase.

Powder flow was assessed using the Hosowaka powder characteristic tester, which involved the use of a number of flow properties; angle of repose, angle of spatula, compressibility, cohesion and adhesion and is based on a technique developed by Carr (1965a). When compared to the micronised salbutamol sulphate the spray dried material flowed less readily, both powders however, were found to be poorly flowing. When mixed with coarser materials, lactose and Avicel®, in concentrations between 0.25 and 5 %w/w, both spray dried and micronised salbutamol sulphate improved flowability index to a maximum after which the flowability index decreased, to a similar degree.

Cascade impactor studies showed the spray dried material to behave in a similar manner to that of the micronised salbutamol sulphate and a proprietary preparation. All three forms of salbutamol sulphate gave MMADs of between 9.6 and 9.8 μm, as
determined by cascade impaction. The high MMADs were thought to be the cause of insufficient deaggregation of the particles on release from the device. Twin impinger analysis showed percentage deposition in stage II for spray dried salbutamol to be lower than that of the micronised salbutamol when liberated from the Rotahaler® but almost equivalent when delivered from the Spinhaler®. This highlighted the importance of the liberation device and its design for dry powder inhaler formulation. In both cases however, stage II deposition was less than 10% and device deposition high. When mixed with a lactose carrier deposition was not seen to be improved but the crudeness of capsule production may have influenced the result.

The surface energies and polarity of spray dried and micronised salbutamol sulphate and medium grade and spray dried lactose were calculated from contact angle measurements, using the Wilhelmy gravitational method (Buckton, 1990). The computated surface energies were subsequently used to calculate the work of cohesion, work of adhesion and spreading coefficients between salbutamol materials and lactose. These were discussed as potential indicators of powder flow and in vitro deposition by comparing values to the experimental data from flow measurements and twin impinger studies. For example, works of cohesion were used to explain the lower percentage deposition in stage II of the spray dried salbutamol sulphate compared to micronised salbutamol sulphate, when tested alone (without a coarse carrier). Spray dried salbutamol sulphate had a higher work of cohesion suggesting that deaggregation between particles, when released from the dry powder aerosol device, to be more difficult and hence higher stage I deposition. The higher the surface energy or attraction between particles the poorer the flowability (Carr, 1965a). This theory was supported by the calculated surface energy values for spray dried and micronised salbutamol sulphate. The surface energy values and subsequent calculation of works of adhesion, cohesion and spreading coefficient showed potential as a possible predictor for dry powder aerosol formulation. However, it should be noted that the results obtained are more useful qualitatively than quantitatively and that further work with other materials is necessary to confirm its use.
All results obtained for the research presented hold true for salbutamol sulphate using a Büchi 190 mini spray dryer with a pneumatic nozzle. The results may not extrapolate to other materials and alternative spray dryers. Also scale up may present unforeseen problems (Nonhabel and Moss, 1971). Scale up based on the research presented, would require a spray dryer that would produce a spray of equivalent droplet size and drying conditions to give the same controlled particle size. (The larger spray dryer the longer the resident time of powder in drying chamber). This noted, spray drying has been shown to be a successful process for controlled particle size reduction producing a material which is at least as equivalent to the micronised material, in terms of size and aerodynamic behaviour.

6.2 Further Work

Although spray drying proved to be useful as a means of controlled particle size production, the powders produced were still cohesive, adhesive and had poor flow properties. Surface energetic work indicated that a reduction in the overall surface energy would lead to a potentially better formulation. For this reason it would seem rational that any future alteration in this technique should be aimed the production of a product with lower surface energy. One potential means to achieving this would be the use of co-spray drying. For example the use of plasticisers in the microencapsulation of theophylline, by spray drying, has shown to alter flow properties of the final microcapsules (Wan et al, 1992). Co-spray drying has also been used to improve powder properties for tableting, by drying a slurry in a type of granulation process (Kornblum, 1969).

An alternative use of co-spray drying would be to spray dry the drug and carrier together. Preliminary work in this area was promising. Plate 6.1 shows an electron micrograph of co-spray dried salbutamol sulphate from a slurry of lactose. The larger particles shown are assumed to be those of lactose as previous spray drying of salbutamol sulphate, under the conditions used, has always produced smaller particles.
Plate 6.1 Co-spray dried salbutamol sulphate and lactose.
The stability of spray dried salbutamol was not investigated because of time constraints. Studies using sodium cromoglycate have shown however, the spray dried material to be less stable to changes in humidity, due to alteration in crystallinity and hence solubility (Vidgren et al, 1989). In vitro, controlled humidity deposition studies described by Martin et al (1988), may therefore, be useful in this area.

Improvements in other areas such as particle sizing could be made. It would be advantageous to measure powder particle size of the aerosol, using laser diffraction, rather than suspended in a liquid. Many on-line, real time, laser diffraction apparatus have been designed for this purpose (Olsson et al, 1988; Sem, 1984).
Appendices
Appendix 1

Reynolds (Re) No. \[ \frac{DV\rho_a}{\mu_a} \]

Prandtl (Pr) No. \[ \frac{C_p\mu_a}{K_d} \]

Schmidt (Sc) No. \[ \frac{\mu_a}{D\rho_a} \]

Nusselt (Nu) No. \[ \frac{h_cD}{K_d} \]

Sherwood (Sh) No. \[ \frac{K_pD}{D_v} \]

Where \( D \)=droplet diameter, \( \rho_a \)=density of drying medium, \( \mu_a \)=viscosity of drying medium, \( C_p \)=heat capacity (constant pressure of drying medium), \( K_d \)=average thermal conductivity of gaseous film surrounding an evaporating droplet, \( h_c \)=convection heat transfer coefficient, \( K_p \)=mass transfer coefficient, \( D_v \)=diffusion coefficient.
Appendix 2

Chemical Properties of Drugs Used

**Salbutamol Base**

Solubility, 1 in 70

Melting Point, 156°C

**Salbutamol Sulphate**

Solubility, 1 in 4

Melting Point, 158-160°C

**Isoprenaline Sulphate**

Solubility, 1 in 4

Melting Point, 128°C
**Isoprenaline Hydrochloride**

Solubility, 1 in 1
Melting Point, 166-170°C

**Pentamidine Isethionate**

Solubility, 1 in 10
Melting Point, 180°C
Appendix 3

Particle Size Distributions for Medium and Intermediate Grade Lactose, Measured using Laser Diffraction.

<table>
<thead>
<tr>
<th>Size (µm)</th>
<th>% under</th>
<th>Particle size distribution (µm)</th>
<th>% under</th>
</tr>
</thead>
<tbody>
<tr>
<td>188.0</td>
<td>100.0</td>
<td>20.6</td>
<td>2.5</td>
</tr>
<tr>
<td>162.0</td>
<td>99.0</td>
<td>18.8</td>
<td>2.4</td>
</tr>
<tr>
<td>140.0</td>
<td>96.1</td>
<td>16.4</td>
<td>2.2</td>
</tr>
<tr>
<td>121.0</td>
<td>91.6</td>
<td>14.1</td>
<td>2.2</td>
</tr>
<tr>
<td>104.0</td>
<td>85.4</td>
<td>11.8</td>
<td>2.0</td>
</tr>
<tr>
<td>97.7</td>
<td>78.2</td>
<td>9.8</td>
<td>1.9</td>
</tr>
<tr>
<td>89.9</td>
<td>71.3</td>
<td>8.6</td>
<td>1.6</td>
</tr>
<tr>
<td>82.3</td>
<td>64.2</td>
<td>7.8</td>
<td>1.3</td>
</tr>
<tr>
<td>77.5</td>
<td>57.3</td>
<td>7.1</td>
<td>1.1</td>
</tr>
<tr>
<td>66.9</td>
<td>49.8</td>
<td>6.3</td>
<td>0.8</td>
</tr>
<tr>
<td>57.7</td>
<td>42.9</td>
<td>5.5</td>
<td>0.6</td>
</tr>
<tr>
<td>49.8</td>
<td>37.1</td>
<td>4.5</td>
<td>0.3</td>
</tr>
<tr>
<td>42.9</td>
<td>31.7</td>
<td>3.8</td>
<td>0.2</td>
</tr>
<tr>
<td>37.1</td>
<td>27.5</td>
<td>3.2</td>
<td>0.1</td>
</tr>
<tr>
<td>32.0</td>
<td>22.9</td>
<td>2.6</td>
<td>0.1</td>
</tr>
<tr>
<td>27.6</td>
<td>20.5</td>
<td>2.3</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Result source Sample
Record No. = 25
Focal length = 100 mm
Volume distribution
Beam length = 25.0 mm
Obscuration = 0.2110
Volume Conc. = 0.0072 %
Log. Diff. = 3.29

Medium Grade Lactose.
Intermediate Grade Lactose.
Appendix 4

Temperature-Solubility Curves for Salbutamol Sulphate, Salbutamol Base and Pentamidine Isethionate.

In Water

Solubility Versus Temperature Profile for Salbutamol Sulphate.

Solubility Versus Temperature Profile for Salbutamol Base.

Solubility Versus Temperature Profile for Pentamidine Isethionate ($R^2=0.967$).

256
References
References

Aerosol Consensus Statement

Andersen Samplers Inc.
Operating Manual for Andersen 1 ACFM non viable ambient particle sizing samplers.
(1985).

Atkins, P.J.
Aerodynamic particle size testing - impinger methods.

Balmes, J.R.
The environmental impact of chlorofluorocarbon use in metered dose inhalers.

Bell, J.H., Hartley, P.S. and Cox, J.S.G.
Dry powder aerosols 1: a new powder inhalation device.

Bell, J.H., Brown, K. and Glasby, J.
Variation in delivery of isoprenaline from various pressurized inhalers.

Blackford, D.B.
Particle size analysis with an aerodynamic particle sizer - a laboratory system and a proposed on line system.

Bowman, W.C. and Rand, M.J.

Bouchikhi, A., Becquemin, M.H., Bignon, J., Roy, M. and Teillac, A.
Particle size study of nine metered dose inhalers, and their deposition probabilities in the airways.

Boyes, R.N.
Prospects for drug therapy via the respiratory tract.
References

British Pharmacopoeia, Volume II

British Pharmacopoeia, Volume I

Physical characterisation of pharmaceutical solids.

Broadhead, J., Rouan, S.K.E. and Rhodes, C.T.
The spray drying of pharmaceuticals.

Brown, R.L.
Flow Properties.

Buckton, G.
The assessment and pharmaceutical importance of solid/liquid and solid/vapour interfaces: a review with respect to powders.

Buckton, G.
Contact angle, adsorption and wettability - a review with respect to powders.

Buckton, G.
The estimation and application of surface energy data for powdered systems.

Buckton, G. and Newton, J.M.
Assessment of the wettability and surface energy of a pharmaceutical powder by liquid penetration.

Buckton, G. and Newton, J.M.
Liquid penetration as a method of assessing the wettability and surface energy of pharmaceutical powders.

Buckton, G. and Newton, J.M.
Assessment of the wettability of powders by use of compressed powder discs.
References

Buckton, G., Choularton, A., Beezer, A.E., Chatham, S.M.
The effect of the comminution technique on the surface energy of a powder.

Buma, T.J. and Henstra, S.
Particle structure of spray dried caseinate and spray dried lactose as observed by a
scanning electron microscope.

Byron, P.R.
Some future perspectives for unit dose inhalation aerosols.

Byron, P.R.
Pulmonary targeting with aerosols.

Carli, F. and Simioni, L.
Limitations of the Washburn equation in quantifying penetration rates.

Carr, R.L.
Classifying flow properties of solids.

Carr, R.L.
Evaluating flow properties of solids.

Castleman, R.A.
The mechanism of the atomisation of liquids.

Chaloud, J.H., Martin, J.B. and Baker, J.S.
Fundamentals of spray drying detergents.

Chan, S.Y. and Pilpel, N.
Absorption of moisture by sodium cromoglycate and mixtures of sodium cromoglycate
and lactose.

Charlesworth, D.H. and Marshall, W.R.
Evaporation from drops containing dissolved solids.
Clarke, S.W.

Corrigan, O.I., and Holohan, E.M.
Amorphous spray dried hydroflumethiazide-polyvinylpyrrolidone systems: physicochemical properties.

Corrigan, O.I., Sabra, K. and Holohan, E.M.
Physicochemical properties of spray dried drugs: phenobarbitone and hydroflumethiazide.

Corrigan, O.I., Holohan, E.M. and Sabra, K.
Amorphous forms of thiazide diuretics prepared by spray drying.

Craik, D.J. and Miller, B.F.
The flow properties of powders under humid conditions

Crooks, M. J. and Ho, R.
Ordered mixing in direct compression of tablets.

Crosby, E.J. and Marshall, W.R.
effects of drying conditions on the properties of spray dried particles.

Cuss, F.M.
Is choice of drug delivery as important as choice of drug in childhood asthma?

Dalby, R.N. and Byron, P.R.
Metered dose inhalers containing flammable propellants: Perspectives and some safety evaluation procedures.

Dalby, R.N., Byron, P.R., Shepherd, H.R. and Papadapoulos, E.
CFC propellant substitution: P-134a as a potential replacement for P-12 in MDIs.
Dan, J. R.
Forces involved in the adhesive process. Critical surface tensions of polymeric solids as determined with polar liquids.

Danish, F.Q. and Parott, E.L.
Flow rates of solid particulate pharmaceuticals.

De Boer, A.H., Buitendijk, H.H., Lerk, C.F. and Vermeulen, J.
Development of dry powder inhalation systems.

Developments in inhalation therapy.

Duffie, J.A. and Marshall, W.R.
Factors influencing the properties of spray dried materials. Part 1.

Duffie, J.A. and Marshall, W.R.
Factors influencing the properties of spray dried materials. Part 11.

Eaves, T and Jones, T.M.
Moisture uptake and tensile strength of bulk solids.

Eaves, T and Jones, T.M.
Effect of moisture in the tensile strength of bulk solids I: Sodium chloride and the effect of particle size.

Edwards, A.M. and Chambers, A.
Comparison of a lactose free formulation of sodium cromoglycate and sodium cromoglycate plus lactose in the treatment of asthma.

El Gindy, N.A. and Samaha, M.W.
Tensile strength of some pharmaceutical compacts and their relation to surface free energy.

Fell, J.T. and Newton, J.M.
The production and properties of spray dried lactose. Part 1.
References

Fell, J.T. and Newton, J.M.
The production and properties of spray dried lactose. Part 2.

Fell, J.T. and Newton, J.M.
The production properties of spray dried lactose, part 3

Fowes, F.M.
Attractive forces at interfaces.

Fox, H.W. and Zisman, W.A.
The spreading of liquids on low energy surfaces. I. Polytetrafluoroethylene.

Garrett, M.J.
A review of the NDA rewrite.

Gonda, I.
A semi-empirical model of aerosol deposition in the respiratory tract for mouth inhalation.

Gonda, I.
Study of the effects of polydispersity of aerosols on regional deposition in the respiratory tract.

Gonda, I.

Gonda, I and Byron, P.R.
Perspectives on the biopharmacy of inhalation aerosols.

Good, R.J. and Girifalco
A theory for estimation of surface and interfacial energies. III Estimation of surface energies of solids from contact angle data.

Good, R.J.
Surface free energy of solids and liquids thermodynamics, molecular forces and structures.
References


Gretzinger, J. and Marshall, W.R.
Characteristics of pneumatic atomisation.
A. I. Ch. E. J. (1961)7:312-318

Hallworth, G.W. and Andrews, U.G.
Size analysis of Suspension inhalation aerosols by inertial separation methods.

Hallworth, G.W.
An improved design of powder inhaler.

Hallworth, G.W. and Westmoreland, D.G.
The twin impinger: a simple device for assessing the delivery of drugs from metered
dose pressurised aerosol inhalers.

Handbook of Pharmaceutical Excipients.
Publ. American Pharmaceutical Association and Pharmaceutical Society of Great

Hansford, D.J., Grant, D.J.W. and Newton, J.M.
The influence of processing variables on the wetting properties of hydrophobic
powder.

Hausner, H.H.
Friction conditions in a mass of metal powder.

Heertjes, P.M. and Kossen, N.W.F.
Measuring contact angles of powder liquid systems.

Hersey, J.A.
Ordered mixing:A new concept in powder mixing practice.

Hicks, J.F. and Megaw, W.J.
The growth of ambient aerosols in the conditions of the respiratory system.

Hiller, C., Mazumder, M., Wilson, D. and Bone, R.
Aerodynamic size distribution of metered dose bronchodilator aerosols

Hiller, F.C., Mazumder, M.K., Wilson, J.D. and Bone, R.C.
Effect of low and high relative humidity on metered dose bronchodilator solution and
powder aerosols.

Hilman, B.
Aerosol deposition and delivery of therapeutic aerosols.

Jones, T.M.
Measuring cohesion in powders.

Kendall, K.
The impossibility of comminuting small particles by compression.

Kendall, K.
Surface energy of solids from ultrasonic studies of particle assemblies.

Kiesvaara, J.
The effect of compression pressure and compression time on the surface free energy
of tablets.

Kim, K.Y. and Marshal, W.R.
Drop-size distributions from pneumatic atomizers.

Kim, C.S., Trujillo, D. and Sackner, M.A.
Size aspects of metered dose aerosols.

King, D., Earnshaw, S.M. and Delaney, J.C.
Pressurised aerosol inhalers: The cost of misuse.

Kirk, W.K.
Invitro method of comparing clouds produced from inhalation aerosols for efficiency
in penetration of airways.
Kirk, W.F.
Aerosols for inhalation therapy.

Kloubek, J.
Development of methods for surface free energy determination using contact angles of liquids on solids.

Kornblum, S.S.
Sustained-action tablets prepared by employing a spray drying technique for granulation.

Kossen, N.W.F. and Heertjes, P.M.
The determination of contact angle for systems with a powder.

Kulvancich, P and Stewart, P.J.
Influence of relative humidity on the adhesive properties of a model interactive system.

Kumar, R. and Prasad, K.S.L.
Studies on pneumatic atomization.

Lerk, C.F., Lagas, M., Boelstra, J.P. and Broersma, P.
Contact angles of pharmaceutical powders.

Contact angles and wetting of pharmaceutical powders.

Luangtana-anan, M. and Fell, J.T.
Surface energetics of powders before and after compaction.

Manning, W.P. and Gauvin, W.H.
Heat and mass transfer to decelerating finely atomised sprays.

Manufacturing Chemist.
Developments in inhalation therapy.
Marshall, W.R. and Madison, W.
Heat and mass transfer in spray drying.

Marshall, W.R. and Seltzer, E.

Marshall, W.R. and Seltzer, E.

Martin, G.P., Bell, A.E. and Marriott, C.

Masters, K

Matsuda, Y., Otsuka, M., Onoe, M. and Tatsumi, E.
Amorphism and physico-chemical stability of spray dried frusemide.

Matthys, H.
Inhalation delivery of asthma drugs.

May, K.R.
Multistage liquid impinger.

Merck Index.
An encyclopedia of chemical drugs and biologicals. 11th edn.
Ed. Budavari, S. Publ. Merck and Co. Inc., Rathway, NY, USA

Mellem, H., Lande, K., Kjeldsen, S.E., Westheim, A., Eide, I., Ekholt, P.F. and Boye, N.P.
Faster and more reliable absorption of adrenaline by aerosol inhalation than by subcutaneous injection.

Montgomery, D.C.
References

Montgomery, A.B., Luce, J.M., Turner, J., Lin, E.T., Debs, R.J., Corkery, K.J., Brunette, E.N., Hopewell, P.C.
Aerosolized pentamidine as sole therapy for pneumocystis carinii pneumonia in patients with acquired immunodeficiency syndrome.

Morën, F.
Dosage forms and formulation for drug administration to the respiratory tract.

Morén, F. and Andersson, J.
Fraction of dose emitted after administration of pressurised inhalation aerosols.

Neumann, A.W., Good, R.J., Hope, C.J. and Sejpal, M.
An equation of state approach to determine surface tensions of low energy solids from contact angles.

Neumann, B.S.

Newman, S.P.
Aerosol physiology, deposition and metered dose inhalers.

Newman, S.P. and Clarke, S.W.
Therapeutic aerosols I-Physical and practical considerations.

Newman, S.P., Killip, M., Pavia, D., Moren, F. and Clarke, S.W.
The effect of changes in particle size on the deposition of pressurized inhalation aerosols.

Newman, S.P., Morén, F., Trofast, E., Talaee, N. and Clarke, S.W.
Deposition and clinical efficacy of terbutaline sulphate from turbohaler, a new multi-dose powder inhaler.

Newman, S.P., Weisz, A.W.B., Talaee, N. and Clarke, S.W.
Improvement of drug delivery with a breath actuated pressurised aerosol for patients with poor inhaler technique.
References

Newton, J.M.
Spray during and its application in pharmaceuticals.

Nonhabel, G. and Moss, A.A.H.
Drying of solids in the chemical industry.

Nyström, C. and Malmqvist, K.
Studies on direct compression of tablets I. The effect of particle size in mixing finely divided powders with granules.

Odidi, I.O., Newton, J.M. and Buckton, G.
The effect of surface treatment on the values of contact angles measured on compressed powder surface.

Correlation between laser scattering and inertial impaction for the particle size distribution characterisation of bricanyl turbuhaler®.

Osterman, K., Stahl, E. and Kallen, A.
Bricanyl Turbuhaler in the treatment of asthma: six week multi-centre study carried out in Sweden, the United Kingdom, Denmark, Norway and Finland.

Paronen, P., Vidgren, M., Kärkkäinen, A. and Karjalainen,P.
Drug particle deposition in respiratory tract after delivery from the dry powder inhaler.

Parsons, G.E., Buckton, G. and Chatham, S.M.
The use of surface energy and polarity determinations to predict physical stability of non-polar, non-aqueous suspensions.

Parsons, G.E., Buckton, G. and Chatham, S.M.
The estimation of solid surface energy from contact angle measurements.
Int. J. Pharm. In press

Persson, G. and Wiren, J.E.
The bronchodilator response from inhaled terbutaline is influenced by the mass of small particles: a study on a dry powder inhaler (Turbuhaler).
References

Pharmaceutical Journal
Astra to launch novel dry powder inhaler.

Pharmaceutical Journal.
New asthma inhaler device.

Phillips, E.M., Bryon, P.R., Fultz, K. and Hickey, A.J.
Optimized aerosol inhalation aerosols II. Inertial testing methods for particle size
analysis of pressurized inhalers.

Pierce, R.J., Seale, J.P. and Ruffin, R.E.
Inhaled respiratory medications and use of chlorofluorocarbons (CFCs).

Pover, G.M., Browning, A.K., Mullinger, B.M., Bulter, A.G. and Dash, C.H.
A new dry powder inhaler.

Pover, G.M. and Dash, C.H.
A new, modified form of inhaler (Rotahaler) for patients with choric obstructive lung
disease.

Pritchard, J.N.
Particle growth in the airways and the influence of air flow in "A new concept in
Medicom, Amsterdam. (1987):3-24,

Ranz, W.E. and Wong, J.B.
Jet impactors for determining the particle size distributions of aerosols.

Ripple, E.G.
Powders in "Remingtons pharmaceutical sciences" 17th edn.

Rowe, R.C.
Correlation between predicted binder spreading coefficients and measured granule and
tablet properties in the granulation of paracetamol.

Rowley, G. and Newton, J.M.
References

Limitations of liquid penetration in predicting the release of drugs for hard gelatin capsules.

Saunders, K.B.
Misuse of inhaled bronchodilator agents.

Schmidt, P.C. and Benke
"Supersaturated" ordered mixtures on the basis of sorbitol.

Sem, G.J.
Aerodynamic particle size: why is it important.

Singh, P., Desai, S.J., Simonelli, A.P. and Higuchi, W.I.
Role of wetting on the rate of drug release from inert matrices.

Sjenitzer, F.
Spray drying, theoretical considerations on the movement and evaporation of liquid droplets, the use of various drying gases and the application of the concept of transfer units to a rational evaluation of the process.

Spelt, J.K., Absolom, D.R. and Neumann, A.W.
Solid surface tension: The interpretation of contact angles by the equation of state approach and theory of surface tension components.

Stamm, A., Gissinger, D. and Boymon, C.
Quantitative evaluation of the wettability of powders.

Staniforth, J.N.
Advances in powder mixing and segregation in relation to pharmaceutical processing.

Staniforth, J.N., Rees, J.E., Lai, F.K. and Hersey, J.A.
Interparticulate forces in binary and ternary ordered powder mixes.

Studebaker, M.L. and Snow, C.W.
The influence of ultimate composition upon the wettability of carbon blacks.

271

Sumby, B.S., Cooper, S.M. and Smith, I.J.
A comparison of the inspiratory effect required to operate the Diskhaler® and the Turbohaler in the administration of powder drug formulations.

Thanomikat, P., Stewart, R.J. and Grover, P.S.
Influence of carrier particle size on prednisolone - direct compression vehicle ordered mixes.

Train, D.
Some aspects of the property of angle of repose of powders.

Valerius, N.H., Koch, C. and Hoiby, N.
Prevention of chronic pseudomonas aeruginosa colonisation in cystic fibrosis by early treatment.

Van Oss, C.J., Chaudhery, M.K., and Good, R.J.
Monopolar surfaces.

Verhey, J.G.P., and Lammers, W.L.
A method for measuring the particle density distribution of spray dried powders.

Vidgren, M., Arppe, J., Vainio, P., Vidgren, P. and Paronen, P.
New Gamma Labelling Technique for metered dose aerosols and dry powder preparations of salbutamol.

Vidgren, M., Kärkkäinen, A. and Karjalainen, P.
In vitro and in vivo deposition of drug particles inhaled from pressurized aerosol and dry powder inhaler.
Drug Dev. Ind. Pharm. (1988b)14(15-17);2649-2665.

Vidgren, M.T., Kärkkäinen, A., Karjalainen and Paronen, T.P.
A Novel labelling method for measuring the deposition of drug particles in the respiratory tract.
Int. J. Pharm. (1987a)37:239-244.

Vidgren, M.T., Kärkkäinen, A., Paronen, T.P. and Karjalainen, P.
Respiratory tract deposition of $^{99m}$Tc-labelled drug particles administered via a dry powder inhaler.

Vidgren, M., Kärkkäinen, A., Karjalainen, P., Paronen, P., Nuutinen, J.
Effect of powder inhaler design on drug deposition in the respiratory tract.

Vidgren, M., Paronen, P., Vidgren, P., Vainio, P. and Nuutinen, J.
Radiotracer evaluation of the deposition of drug particles inhaled from a new powder inhaler.

Vidgren, M.T., Vidgren, P.A. and Paronen, T.P.
Comparison of physical and inhalation properties of spray dried and mechanically micronized disodium cromoglycate.
Int. J. Pharm. (1987c)35:139-144.

Vidgren, M., Vidgren, P., Uotila, J. and Paronen, P.
In vitro inhalation of disodium cromoglycate powders using two dosage forms.

Vidgren, M., Vidgren, P. and Paronen, P.
In vitro deposition of disodium cromoglycate particles inhaled from two dry powder devices.

Vidgren, P., Vidgren, M. and Paronen, P.
Physical stability and inhalation behaviour of mechanically micronised and spray dried disodium cromoglycate in different humidities.

The fate of $^{14}$C disodium cromoglycate in man.

Wan, L.S.C., Heng, P.W.S., and Chia, Cecilia.
Plasticizers and their effects on microencapsulation process by spray drying in an aqueous system.

Washburn, E.W.
The dynamics of capillary flow.
Wong, L.W. and Pilpel, N.
Effect of particle shape on the mixing of powders.

Wright, P.J.
The surface properties of films of gelatin and effects of the inclusion of hydrophobic

Wu, S.
Polar and non polar interactions in adhesion.

Yang, Y., Zografi, G. and Miller, E.E.
Capillary flow phenomena and wettability in porous media. II Dynamic flow studies.

York, P.
Powder failure testing - pharmaceutical applications.

Young, T.
An essay on the cohesion of fluids.
Phil. Trans. R. Soc. (1805)95:65-87.

Young, S.A. and Buckton, G.
Particle size growth in aqueous suspensions: the influence of surface energy and
polarity.

Zajic, L. and Buckton, G.
The use of surface values to predict optimum binder selection for granulations.

Zografis, G. and Johnson, B.A.
Effects of surface roughness on advancing and receding contact angles.

Zografis, G. and Tam, S.S.
Wettability of pharmaceutical solids: estimates of solid surface polarity.