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Production of spray dried salbutamol sulphate for use in dry powder aerosol formulation

A. Chawla [a], K.M.G. Taylor [a,*], J.M. Newton [a], M.C.R. Johnson [b]

[a] *Centre for Materials Science, School of Pharmacy, University of London, 29–39 Brunswick Square, London WC1N 1AX, UK,*
[b] *Dagenham Research Centre, Rhône-Poulenc Rorer Ltd, Dagenham RM10 7XS, UK*

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Abstract

Salbutamol sulphate particles, for use in dry powder aerosol formulation, were prepared by spray drying, using a Büchi 190 mini spray dryer. The spray drying parameters were investigated in relation to particle size and yield of the resultant powder. Important factors were determined using a 2^4 factorial statistical design. The four factors investigated were pump speed, aspirator level (the rate at which the drying air is pulled through the dryer), inlet temperature and the concentration of the aqueous salbutamol sulphate solution dried. Spray drying conditions were chosen based on results from the experimental design and working knowledge of the spray dryer, to produce a batch of salbutamol sulphate powder on which further studies were performed. The physicochemical properties of spray dried salbutamol sulphate were compared to those of the micronised drug. Infrared spectroscopy, X-ray diffraction, appearance, particle size analysis (including aerodynamic diameter) and powder flow were investigated. It was found that spray drying produced spherically shaped particles of salbutamol sulphate having a mass median diameter of 4.5 μm (laser diffraction), mean Feret's diameter (image analysis) of 1.58 μm and a mass median aerodynamic diameter of 9.7 μm (cascade impaction), i.e., particles sufficiently small in diameter for use in inhalation formulation. The spray dried material was seen to perform as well as the micronised material in most cases with the exception of powder flow properties, where performance was slightly poorer.

Key words: Aerosol; Dry powder inhaler; Particle; Particle size; Physicochemical properties; Salbutamol sulfate; Spray drying

1. Introduction

Dry powder inhalers (DPIs) are a popular means of delivering anti-asthmatic drugs. Unlike pressurised metered dose inhalers (MDIs), DPIs are breath actuated, consequently there is no need for breath-actuation co-ordination, making them particularly appropriate for use by children (Cuss, 1988). Being portable, easy to use and free of chlorofluorocarbon propellants and other excipients (except for a lactose carrier, present in some formulations) it is likely that they will be increasingly used in the future.

A major formulation consideration in the manufacture of therapeutic aerosols is that of particle

* Corresponding author.

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size reduction. It is well documented that particles of less than 10 μm are required to penetrate and deposit in the lung. There are many conflicting references to the ideal size for deposition in the peripheral airways, but it is generally regarded to be between 0.8 and 5 μm (Gonda, 1988; Aerosol Consensus Statement, 1991; Hillman, 1991). Powders with particle sizes in this range are characteristically cohesive and adhesive with poor flow properties (Byron, 1986). Traditionally, powders have been reduced to a respirable size by micronisation, which is a lengthy process, where pre-milling is often required.

Spray drying was investigated in this study as an alternative method of controlled particle size production, having the advantage of being a single-stage process that can be completely controlled by a single operator. Spray drying is a well established dying process (Masters, 1991), traditionally used for thermolabile materials. It has been used successfully in many industries, including the pharmaceutical industry, to produce products of well defined physical and chemical properties.

Studies by Vidgren et al. (1987a,b, 1989) have indicated that spray drying may be an alternative means for the production of sodium cromogylcate particles for dry powder inhalation. In this study spray drying was investigated as a potential method for the production of particles of salbutamol sulphate, a β_2-adrenoceptor stimulant used in the treatment of bronchial asthma. A factorial experimental design was employed as such an approach is valuable in processes, such as spray drying, where it is necessary to study the joint effects of a number of factors on a response (Fell and Newton, 1971). Each factor is investigated in relation to other factors, that is, all factors are 'crossed'. In a series of experiments, all possible combinations of factors at different levels are investigated and the effect, i.e., the change in response produced by a change in the level of the factors, is determined. Several general assumptions are made when employing a factorial design (Montgomery, 1984): all factors are fixed, designs are completely randomised and the response is approximately linear over the range of the factor levels chosen.

The spray drying process and its influence on the powder produced in terms of the factors which are important for dry powder aerosol formulation have been investigated.

2. Materials and methods

2.1. Spray drying

A Büchi 190 mini spray dryer (Büchi Laboratory-Techniques, Switzerland) with a 7 mm pneumatic nozzle was chosen as a method of controlled particle size reduction and to modify the physical properties of salbutamol sulphate. A 2^4 factorial design was employed to investigate which factors concerned with the spray drying process influenced the particle size and percentage yield of the dried product. The four factors investigated were pump speed (the rate at which the feed solution is pumped into the dryer), aspirator level (the rate at which the drying air is drawn through the apparatus), inlet temperature (the temperature at which the feed solution enters the dryer) and concentration of the aqueous salbutamol sulphate feed solution. The levels investigated for each factor are given in Table 1.

The percentage yield was also calculated from the weight of the product collected in the collection vessel of the spray dryer.

Following analysis of the results of the factorial design experiments, conditions were chosen to spray dry a 10% w/v solution of salbutamol sulphate on which further studies were performed. The Büchi 190 mini spray dryer was used with the following parameters: pump speed, 7 ml min^{-1}; air flow rate, 800 l h^{-1}; aspirator level, 18;

Table 1
Factors and the levels used in the experimental factorial design

Notation	Factor	Levels investigated
A	pump speed (ml min^{-1})	5, 7
B	aspirator level	10, 18
C	heat control (°C)	150, 180
D	concentration of salbutamol sulphate (% w/v)	10, 20

inlet temperature, 151–153°C and outlet temperature, 80–85°C.

2.2. Particle shape

The spray dried salbutamol sulphate and micronised powder were viewed using a Phillips XL20 scanning electron microscope (Phillips, Cambridge, U.K.) at an accelerating voltage of between 10 and 15 kV. Electron micrographs taken were subsequently used for computer image analysis of the spray dried product.

2.3. Crystal and chemical structure

The crystal structure of both the micronised and spray dried drug was determined using X-ray powder diffractometery (Phillips PW1820 diffractometer, Phillips, Cambridge, U.K.)

To investigate whether salbutamol sulphate was chemically altered during the spray drying process, infrared spectroscopy was employed. Potassium bromide disks of micronised and spray dried material were scanned over a wavelength range of 800–3600 nm (Perkin Elmer 841 infrared spectrometer, Perkin Elmer Corp., Germany) and compared to the standard given in the British Pharmacopoeia (1993a).

2.4. Particle size distribution

The mass median particle size and size distribution of micronised and spray dried salbutamol sulphate were measured by laser diffraction (Malvern 2600c, Malvern Instruments, Malvern, U.K.). The particles were suspended in cyclohexane (BDH Ltd, Poole, U.K.) by sonication for 30 s before measurement. Computer image analysis (Seescan TPL6v00) was also performed on the electron micrographs of spray dried salbutamol sulphate to produce a mean Feret's diameter.

2.5. In vitro aerosol deposition

50–60 mg of micronised or spray dried salbutamol sulphate, accurately weighed, was manually filled into hard gelatin capsules (size 3). Capsules were placed in a Rotahaler® (Glaxo), and the liberated powder drawn through an Andersen cascade impactor (1 ACFM non-viable ambient particle sizer) operated at a flow rate of 28.3 l min^{-1}. Deposited powder was dissolved in deionised water and assayed for salbutamol sulphate by UV absorbance at 274 nm. A plot of amount of salbutamol sulphate deposited on each stage of the impactor against the effective cut-off diameter for that stage allowed calculation of the mass median aerodynamic diameters (MMAD) of both the spray dried and micronised salbutamol sulphate.

In vitro determination of the respirable fraction of the dose, i.e., the dose predicted to deposit in the lower lung, was measured using the twin-stage liquid impinger (TSI), (BP, 1993b), which has an effective cut-off diameter of 6.4 μm for the lower stage. The percentage of the total dose collected (device + stage one + stage two) in stage two of the impinger was taken to be the respirable fraction. The powders were liberated from a dry powder aerosol device, the Spinhaler® (Fisons), into the throat of the TSI operated at an air flow rate of 60 l min^{-1}.

2.6. Flow properties

Due to the cohesive and adhesive nature of fine particulate powders, the powder flow of spray dried and micronised salbutamol sulphate was measured indirectly. Spray dried and micronised salbutamol sulphate was mixed in concentrations of 0–5% w/w with medium grade lactose (mass median diameter = 52.6 μm) using a Turbula mixer (Type T2C) (90 rpm, 30 min) with coarse sieving after the first 10 min. The powder flow properties of the mixtures were subsequently measured using the Hosokawa Powder Characteristic Tester (Hosokawa Micrometrics Laboratory, Japan) which is based on a method of flowability measurement described by Carr (1965). The instrument provides a method whereby reproducible measurements of angle of repose, angle of spatula, compressibility (which is based on bulk and packed densities) and cohesiveness or uniformity can be made whilst removing operator bias. Each flow measurement was assigned an index number determined by its measured value.

The summation of these values gave a measure of flowability; the higher the flowability value the better the flow of the material being investigated.

3. Results and discussion

3.1. Spray drying

Spray drying was employed in this research as a means of controlled particle size production from an aqueous solution of the drug. It was found, within the limitations of the experimental design, that no sole factor from those tested in the spray dying process was responsible for controlling the particle size of the dried product (Table 2). However, the interaction between the aspirator level and feed solution concentration did affect particle size (95% confidence). That is, when both the aspirator level and the feed concentration were at their highest level, a larger particle size resulted. This would be expected as the concentration of the material in the atomized

Table 2
Results from the factorial design analysis, using particle size data

Source of variation	Contrast	Sum of squares	Degrees of freedom	Mean square	F_o
A	−4.9	0.75	1	0.75	0.22
B	−6.1	1.16	1	1.16	0.34
AB	−4.7	0.69	1	0.69	0.2
C	−15.3	7.32	1	7.32	2.17 [a]
AC	+2.1	0.14	1	0.14	0.04
BC	−7.5	1.76	1	1.76	0.52
ABC	+5.1	0.81	1	0.81	0.24
D	+17.9	10.01	1	10.01	2.97 [a]
AD	−0.7	0.02	1	0.02	5.9×10^{-3}
BD	+24.5	18.76	1	18.76	5.57 [b]
ABD	−10.9	3.72	1	3.72	1.11
CD	+1.7	0.09	1	0.09	0.027
ACD	+2.3	0.16	1	0.16	0.049
BCD	−9.7	2.94	1	2.94	0.87
ABCD	+6.1	1.16	1	1.16	0.34
Error	–	53.86	16	3.37	–
Total	–	103.35	31	–	–

[a] 75% confidence; F_o is greater than or equal to 1.45.
[b] 95% confidence; F_o is greater than or equal to 4.49.

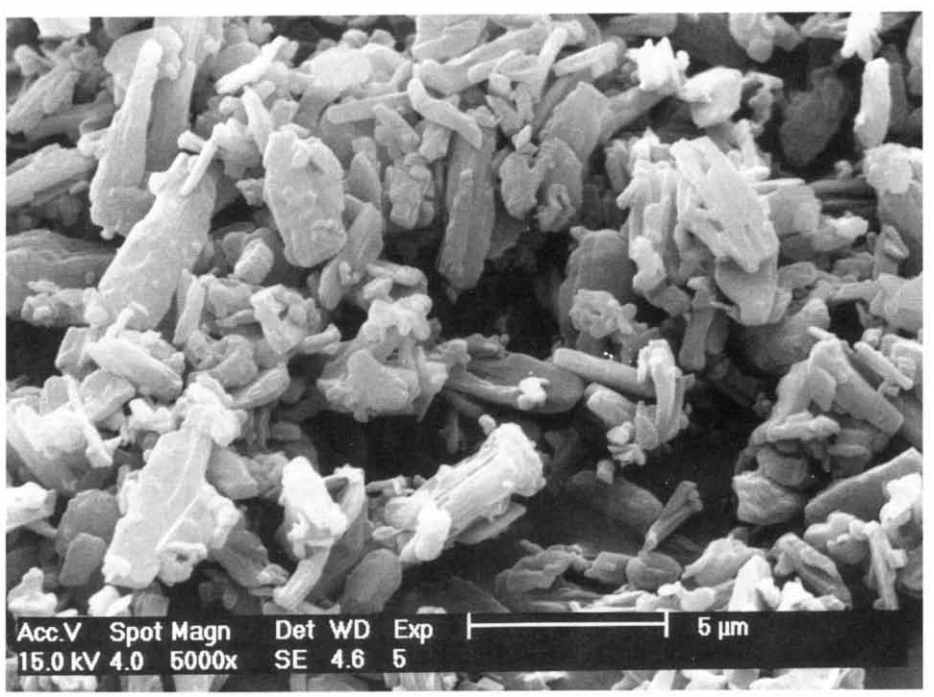

Fig. 1. Electron micrograph of micronised salbutamol sulphate.

droplet would be greater, combined with the effect of increased airflow which would result in a reduced drying time, so reducing shrinkage and thus increasing particle size.

The percentage yield of the spray dried material was affected (95% confidence) by the following factors; the aspirator level, the feed concentration and the interaction between the pump and the feed concentration (Table 3). An increase in any of these factors, or interacting factors, led to an increase in product yield.

Factorial design analysis proved to be a useful means for the evaluation of the spray drying process. However, it should be appreciated that these results are applicable only to the spray drying of salbutamol sulphate in a Büchi mini spray dryer.

3.2. Particle shape

The scanning electron micrograph of mechanically micronised salbutamol sulphate (Fig. 1)

Table 3
Results from the factorial design analysis, using percentage yield data

Source of variation	Contrast	Sum of squares	Degrees of freedom	Mean square	F_0
A	+69.25	149.86	1	149.86	1.59
B	+134.83	568.10	1	568.10	6.04 [a]
AB	−15.18	7.20	1	7.20	0.08
C	−47.11	69.35	1	69.35	0.74
AC	+130.74	534.24	1	534.24	5.68 [a]
BC	+25.17	19.80	1	19.80	0.21
ABC	−36.81	42.34	1	42.34	0.45
D	+158.83	788.34	1	788.34	8.38 [b]
AD	+40.81	52.05	1	52.05	0.55
BD	−44.89	62.97	1	62.97	0.70
ABD	+21.25	14.11	1	14.11	0.15
CD	−58.83	108.16	1	108.16	1.15
ACD	−64.81	131.26	1	131.26	1.39
BCD	−3.11	0.302	1	0.302	3.0×10^{-3}
ABCD	+54.74	93.67	1	93.67	1.00
Error	–	1505.98	16	94.12	–
Total	–	4147.73	31	–	–

[a] 95% confidence; F_0 is greater than or equal to 4.49.
[b] 97.5% confidence; F_0 is greater than or equal to 6.12.

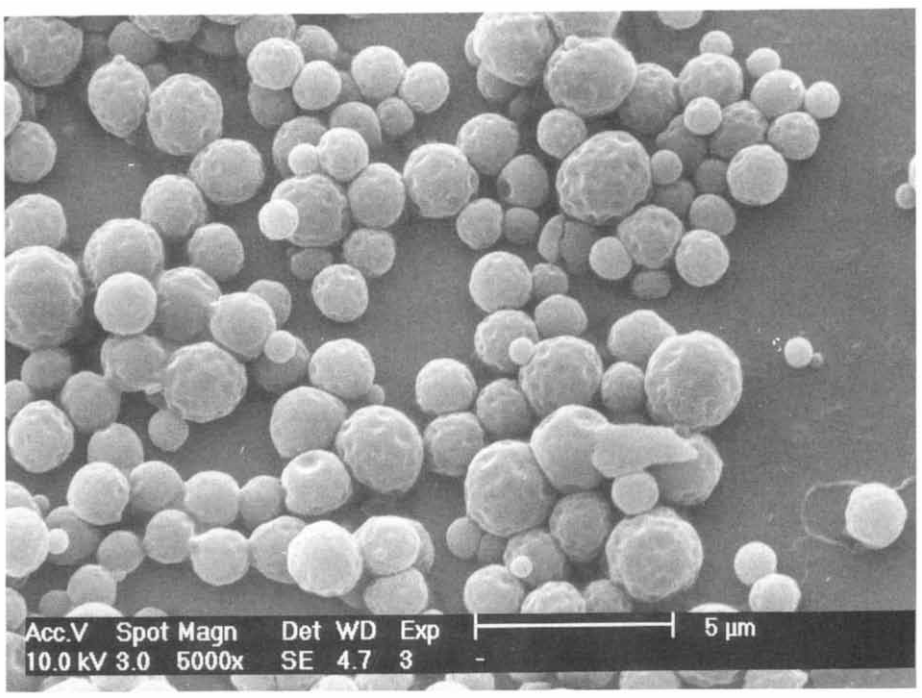

Fig. 2. Electron micrograph of spray dried salbutamol sulphate.

showed the powder to be typical of a crystalline material, needle-like in structure. Many irregular particles with much fragmentation were observed. The electron micrographs of the spray dried material (Fig. 2), however, indicated reduced crystallinity with uniform, spherically shaped particles. Some pitting and shrunken areas on the particle surfaces were observed. All the particles observed with the electron micrograph were less than 5 μm in diameter.

3.3. Crystal and chemical structure

The X-ray diffraction patterns (Fig. 3) confirmed the observations made by electron microscopy. Spray drying decreased the crystallinity of the salbutamol sulphate, changing it from a crystalline structure to that of an amorphous one. This is in agreement with previous work in which spray drying has been shown to decrease crystallinity (Corrigan and Holohan, 1984; Corrigan

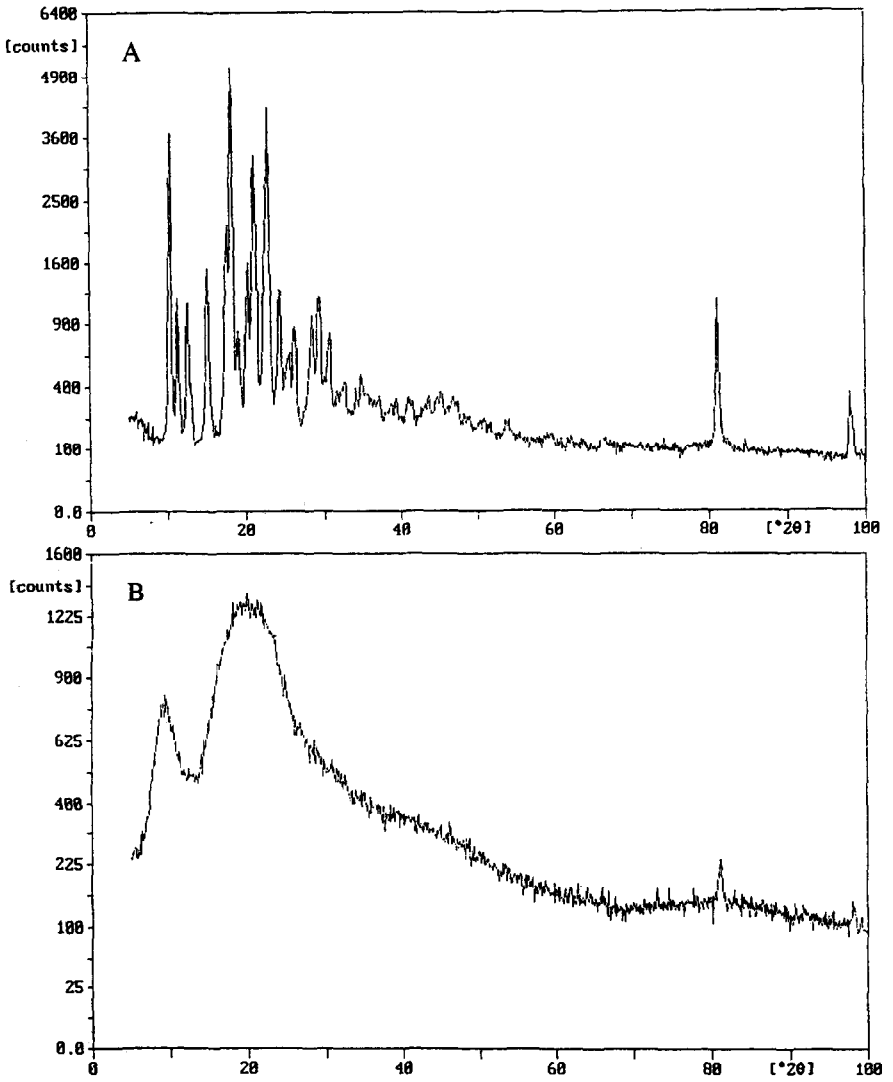

Fig. 3. X-Ray diffraction patterns of (A) micronised and (B) spray dried salbutamol sulphate.

et al., 1984; Vidgren et al., 1987a; Matsuda et al., 1992).

The infrared spectra of the spray dried and micronised salbutamol sulphate were compared to pharmacopoeial reference spectra (British Pharmacopoeia, 1993a). Spray drying did not appear to alter salbutamol sulphate chemically.

3.4. Particle size distribution

The spray dried and micronised drug had similar mass median diameters of 4.4 and 4.7 μm, respectively, as measured by laser diffraction. Spray dried material, however, had a narrower size distribution calculated as the coefficient of spread (90% undersize divided by 50% undersize). Calculated coefficient of spread values for micronised and spray dried salbutamol sulphate were 1.72 and 1.62, respectively.

Image analysis could not distinguish sufficiently between the irregularly shaped crystals of micronised salbutamol sulphate to permit accurate determination of size. Image analysis of the electron micrographs of spray dried drug gave a mean Feret's diameter of 1.58 μm (the total number of particles counted was 823).

3.5. In vitro aerosol deposition

Results from the cascade impactor showed the MMADs of spray dried and micronised salbutamol sulphate to be 9.7 and 9.6 μm, respectively, which compared well with the lactose carrier-based proprietary preparation (Ventolin Rotacaps® (Glaxo) which gave a MMAD of 9.8 μm. These values are greater than would expected from the particle size seen on the electron microscope and measured by laser diffraction. However, the cohesive and adhesive nature of the particles, together with the relatively low air flow rate through the impactor, may have led to deposition and hence sizing of particle aggregates rather than individual particles.

The percentage respirable fractions of the aerosols liberated from the Spinhaler®, as assessed using the TSI, were not significantly different ($p = 0.0005$); 7.63 ± 3.02 and 10.36 ± 6.76% for the spray dried and micronised salbutamol sulphate, respectively. It can be concluded, therefore, that the spray dried material behaves as well as the micronised material in in vitro studies measuring aerodynamic performance and deaggregation behaviour.

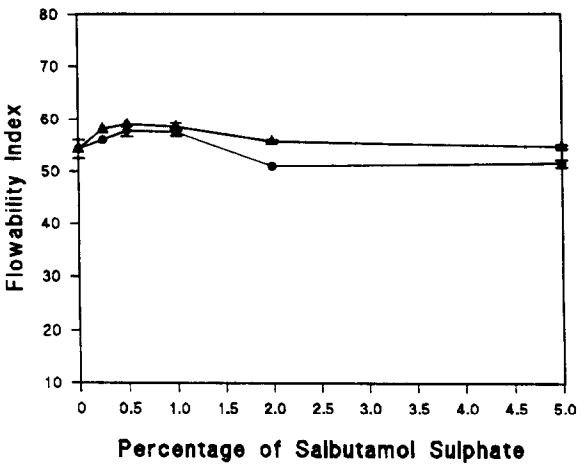

Fig. 4. Flowability of lactose-salbutamol sulphate mixtures: (▲) micronised salbutamol sulphate; (●) spray dried salbutamol sulphate.

3.6. Flow properties

Powder flow is important in dry powder aerosol formulation for both the filling of gelatin capsules or devices and for subsequent release of drug from the dry powder inhaler. Fig. 4 shows graphically the flowability of the lactose mixtures as determined using the Hosokawa Powder Characteristic Tester. At lower concentrations, addition of either spray dried or micronised material increased the flowability index (the greater the flowability index the better the powder flow). The micronised salbutamol sulphate improved flow to a greater degree than the spray dried material. A maximum value was reached whereby further addition of the drug to the lactose mixture caused a reduction in flowability. This can be explained by the fact that at higher drug concentrations, the flow properties of the drug have a greater influence on the total flowability of the mixture. Neither form of the drug was observed to have good flow properties, which is characteristic of powders containing particles in this size range. It

would, however, be expected that the spray dried material would have better flow properties than that of the micronised material because of its spherical nature (Carr, 1965), there being fewer points for physical contact. The poor flowability may have been due to differences in the surface energies of the two materials (Chawla et al., 1993). Additionally, although spherical, the surfaces of the spray dried salbutamol sulphate particles were pitted, increasing the total surface area for contact between particles.

3.7. Conclusion

Spray drying a solution of salbutamol sulphate produces a fine powder of spherically shaped particles, with a mean size appropriate for pulmonary delivery. Spray drying did not alter the drug chemically, but did reduce crystallinity. The spray dried powder was seen to perform as well as micronised drug in in vitro aerosol deposition studies. Spray drying, therefore, provides a useful means of controlled particle size production whereby the physical nature of the drug is well defined.

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References

Aerosol Consensus Statement. *Chest,* 110 (1991) 1106–1109.

British Pharmacopoeia, Vol. I, Reference Spectra, HMSO, London, 1993a, S112.

British Pharmacopoeia, Vol. II, Pressurised inhalations: Deposition of the emitted dose, HMSO, London, 1993b, Appendix XV11C, A193.

Byron, P.R., Some future perspectives for unit dose inhalation aerosols. *Drug Dev. Ind. Pharm.*, 12 (1986) 993–1015.

Carr, R.L., Classifying flow properties of solids. *Chem. Eng.*, 72 (1965) 69–72.

Chawla, A., Buckton, G., Taylor, K.M.G., Newton, J.M. and Johnson, M.C.R., Surface energy determinations of powders for use in dry powder aerosol formulations. *J. Pharm. Pharmacol.*, (Suppl.) 45 (1993) 1148.

Corrigan, O.I. and Holohan, E.M., Amorphous spray dried hydroflumethiazide-polyvinyl pyrrolidine systems. *J. Pharm. Pharmacol.*, 36 (1984) 217–221.

Corrigan, O.I., Holohan, E.M., Sabra, K., Amorphous forms of diuretics prepared by spray drying. *Int. J. Pharm.*, 18 (1984) 195–200.

Cuss, F.M., Is choice of drug delivery as important as choice of drug in childhood asthma? *Agents Actions,* (Suppl.) 23 (1988) 277–283.

Fell, J.T. and Newton, J.M., The production and properties of spray dried lactose: 1. *Pharm. Acta Helv.*, 46 (1971) 226–235.

Gonda, I., Therapeutic aerosols in pharmaceutics. In Aulton, M.E. (Ed.), *The Science of Dosage Form Design,* Churchill Livingstone, London, 1988, pp. 341–358.

Hillman, B., Aerosol deposition and delivery of therapeutic aerosols. *J. Asthma,* 28 (1991) 239–242.

Masters, K., *Spray Drying Handbook,* 5th Edn, Longmans, New York, 1991.

Matsuda, Y., Otsuka, M., Onoe, M. and Tatsumi, E., Amorphism and physical stability of spray dried frusemide. *J. Pharm. Pharmacol.*, 44 (1992) 627–633.

Montgomery, D.C., *Design and Analysis of Experiments,* Wiley, Singapore, 1984, pp. 261–292.

Vidgren, M.T., Karkkainen, A., Karjalainen, P and Paronen, T.P., A novel labelling method for measuring the deposition of drug particles in the respiratory tract. *Int. J. Pharm.*, 37 (1987b) 239–244.

Vidgren, M.T., Vidgren, P.A. and Paronen, T.P., Comparison of physical and inhalation properties of spray dried and micronised disodium cromoglycate. *Int. J. Pharm.*, 35 (1987a) 139–144.

Vidgren, P., Vidgren, M.T. and Paronen, T.P., Physical stability and inhalation behaviour of mechanically micronised and spray dried disodium cromoglycate in different humidities. *Acta. Pharm. Fenn.*, 98 (1989) 71–78.