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Comparison of physical and inhalation properties of spray-dried and mechanically micronized disodium cromoglycate *

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Summary

The physical properties and in vitro inhalation behaviour of mechanically micronized and spray-dried disodium cromoglycate were compared. Spray-dried particles were found to be smaller than micronized particles, mainly in the range 1–5 μm. During the spray-drying process, spherical particles were formed. According to X-ray diffractometric analysis, spray-drying led to an amorphous crystal structure rather than to the crystalline structure of mechanically micronized disodium cromoglycate. The amorphous form was observed to dissolve in phosphate buffer solution at a somewhat higher rate than the crystalline form. During the in vitro inhalation test, a greater percentage of spray-dried disodium cromoglycate than of mechanically micronized disodium cromoglycate reached simulated alveoli 1–3 μm in size, which are therapeutically the most significant. On the basis of its physical properties, spray-dried disodium cromoglycate would seem capable of being used in inhalation therapy. During in vitro inhalation testing, it proved somewhat superior to micronized disodium cromoglycate.

Introduction

Spray-drying processes have been widely used to modify pharmaceutical materials in various ways. Changes resulting from spray-drying can be recorded on the basis of particle properties, e.g. particle size and shape, and on the basis of specific surface area (Corrigan et al. 1983). It is therefore possible to produce powders adapted to various drug manufacturing processes. Alterations in crystal structure can also be induced during spray-drying. Various unstable or metastable polymorphic or amorphous drug forms can be formed. The technological and biopharmaceutical properties of these forms are often dramatically different from those of the original crystal form of the drug. So far, the attention has been paid in these less stable crystal forms to modifying the dissolution properties of solid drug materials (Kawashima et al., 1975).

Disodium cromoglycate is an antiallergic drug commonly used in inhalation therapy. It is believed to act by inhibiting the release of chemical mediators, especially histamine, from sensitized mast cells. Particle size distribution is an important parameter in inhalation therapy. The

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accepted optimum size for inhaled drug particles is between 0.5 and 7 μm (Davies et al., 1976). Particles larger than 7 μm cannot enter the alveoli. Particles smaller than 0.5 μm seem to be exhaled. Dry powder inhalation therapy has become popular as an alternative to aerosol therapy. By using drugs in the dry-powder drug form, the effects of propellants can be avoided. Patient compliance in relation to dry-powder forms of drugs is often better than that in relation to aerosol forms (Paterson and Crompton, 1976).

Because of cohesive forces between micronized particles, dry-powders normally need to be formulated with carrier particles markedly larger than the drug particles. Lactose is the most commonly used carrier. During inhalation, the smaller drug particles separate from the carrier particles and are deposited in the alveoli. This separation stage is the most critical phase from the point of view of drug response (Bell et al., 1971).

As far as the authors know, no reports concerning spray-drying of disodium cromoglycate in relation to inhalation therapy have yet been published. The object of this study was to determine whether or not small enough disodium cromoglycate particles of sufficiently regular shape for use in inhalation therapy were obtainable using a spray-drying process. Special attention was paid to the utility of the particles in a dry-powder dosage form in which lactose was used as a carrier.

Materials and Methods

Disodium cromoglycate (B.P. 1980, Chemisell, Italy) was micronized mechanically using an air jet mill (Fryma type JMRS 80, Switzerland). The micronized material was kept in a desiccator containing silica gel during the test period to prevent uptake of moisture by the drug. Very finely ground (325 mesh) α-lactose monohydrate (Ph. Eur.), used as carrier in the dry-powder mixtures, was supplied by De Melkindustrie, Veghel, The Netherlands.

Spray-drying

Micronized disodium cromoglycate was dissolved in a 6% (2 : 8) (w/v) ethanol/water solution. The solution was spray-dried on a laboratory scale (Büchi Minispray drier type 190, F.R.G.). During drying, the air input temperature was about 180°C. The outlet temperature was about 80°C. The throughput of air was 2.4 m^3/min. 450 ml of drug solution were fed at a rate of 60 ml/min and dried at a nozzle air pressure of 800 Nl. Immediately after drying, the material was placed in a desiccator containing silica gel.

Chemical and crystal structure

The chemical structures of mechanically micronized and spray-dried disodium cromoglycate were determined by means of mass spectrometry (Jeol mass spectrometer type JMS D 300, Japan). Crystal structures of micronized and spray-dried materials were studied by means of X-ray powder diffractometry (Dron diffractometer type 3, U.S.S.R.). Infrared spectra (Perkin Elmer spectrophotometer type 781, U.S.A.) was also obtained.

Particle and powder properties

Mean particle sizes and size distributions were determined using a microscopic method in which the Feret diameters of 400 particles were measured. The mean surface-volume diameter (D_{sv}) of the 400 particles was calculated from Eqn. 1 (Allen, 1975):

$$D_{sv} = \frac{\sum N_i D_i^3}{\sum N_i D_i^2} \quad (1)$$

where N_i is the number of particles of diameter D_i. A unit volume of particles of diameter D_{sv} has an apparent total surface area identical to that of a unit volume of the actual sample.

The shapes of the particles were studied from scanning electron micrographs. These were taken at an accelerating voltage of 15 kV (Jeol electron microscope type JSM 35, Japan). The shape factor (F_s) of the particles was calculated using the Eqn. 2. (Allen, 1975):

$$F_s = D_{sv} \cdot \rho_t \cdot S_w \quad (2)$$

where ρ_t is the effective particle density and S_w is the specific surface area. The larger the value of

F_s, the more irregular the particle shape.

The effective particle density of the materials was determined using an air comparison pycnometer (Beckman type 930, U.S.A.), with helium as the inert gas. Five determinations were undertaken in each case.

The specific surface area (S_w) per unit weight of the powder samples was determined by the BET method from the adsorption of nitrogen gas at the boiling point of liquid nitrogen (Orr Surface Area, Pore Volume Analyzer type 2100E, U.S.A.). Four determinations were undertaken.

Dissolution properties

The dissolution rates of the materials were determined using the paddle method. 250 mg of each powder sample was suspended in 250 ml of phosphate buffer (pH 7.4) at 37°C. The three-bladed stirrer mixed the solution at 40 rpm. Samples taken at various times during the 1 h test were analysed spectrophotometrically at 326 nm (Hitachi type 220 spectrophotometer, Japan).

Inhalation behaviour

The inhalation behaviour of micronized and spray-dried disodium cromoglycate was tested using 1 : 1 lactose/drug mixtures. 10 g of lactose and 10 g of drug were mixed for 15 min in a 250 ml glass vessel (Turbula type 2P mixer, Switzerland). 40 g of the mixed powder per capsule were filled into hard gelatin capsules (number 01). The drug dose was delivered to the air flow using a commercially available powder inhaler (J.S.F. Inhalatore, Italy). The powder inhaler was connected to a Sierra-Andersen sampler (Sierra-Andersen 1 ACFM Nonviable Ambient Particle Sizing Sampler, U.S.A.) fitted with a vacuum pump and air flow meter. The human respiratory cycle was imitated using an air flow of 60 l/min and an air flow period of 2 s. After inhalation of 5 capsules, the 8 stages of the sampler were carefully washed with purified water. After evaporating the water, the samples were diluted to volume with phosphate buffer and analysed spectrophotometrically.

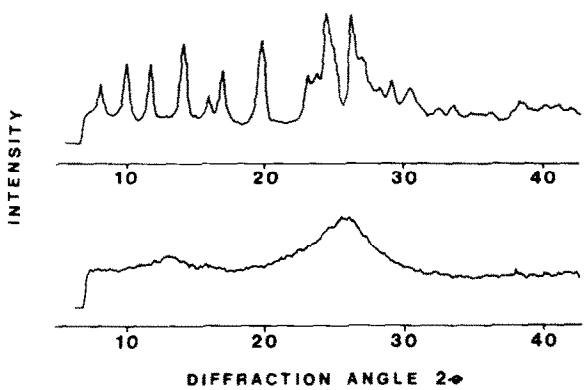

Fig. 1. X-Ray diffraction patterns for mechanically micronized (upper curve) and spray-dried (lower curve) disodium cromoglycate.

Results and Discussion

Chemical and crystal structures

The mass spectra of mechanically micronized and spray-dried disodium cromoglycate were identical. Thus the drug had not decomposed during the spray-drying process.

The infrared spectrum of spray-dried disodium cromoglycate showed some differences, typical of changes in crystal structure, from that of the mechanically micronized drug. The results of powder diffractometry studies confirmed changes in crystal structure. The X-ray diffraction patterns for spray-dried disodium cromoglycate indicated that crystallinity had been markedly degraded and an amorphous structure formed (Fig. 1). Thus molecules of the mechanically micronized drug are bound to each other much more tightly and in a more organized fashion than the molecules of the spray-dried drug.

TABLE 1

Physical properties of mechanically micronized and spray-dried disodium cromoglycate

	D_a (μm)	D_{sv} (μm)	ρ (g/cm^3)	S_w (m^2/g)	F_s
Micronized	3.81 ± 0.084	5.44	1.79	4.4	42.85
Spray-dried	2.81 ± 0.043	3.35	1.82	2.0	12.19

D_a = arithmetic mean diameter (± S.E.); D_{sv} = surface/volume diameter; ρ_t = effective density; S_w = specific surface area; F_s = shape factor.

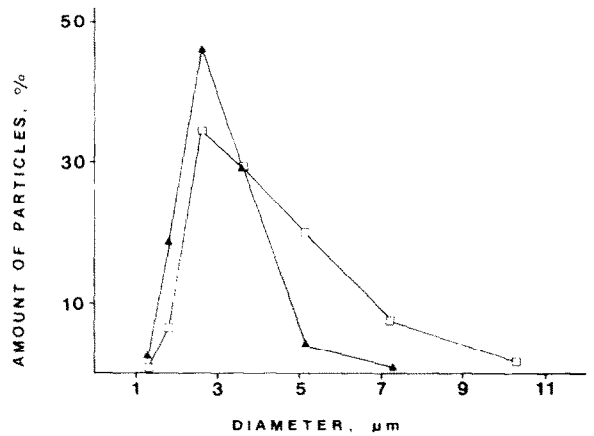

Fig. 2. Particle size distribution of mechanically micronized (□) and spray-dried (▲) disodium cromoglycate, measured microscopically ($n = 400$).

Particle and powder properties

The effective particle densities of the materials studied differed slightly (Table 1), perhaps because of the changes in crystal structure during the spray-drying process.

The particle size data in Fig. 2 and in Table 1 show that spray-drying decreased the average particle size and narrowed the range of particle sizes. As regards the usefulness of the drug in inhalation therapy, it is particularly significant that the number of particles larger than 7 μm having large volumes has decreased. The surface/volume diameter values indicate that spray-dried disodium cromoglycate powder is made up of particles corresponding to smaller spherical particles than the mechanically micronized drug. Theoretically, at least, therefore, a greater volume of the drug should be able to reach and remain in the pulmonary alveoli.

According to the scanning electron micrographs (Fig. 3), the mechanically micronized drug is in the form of typical crystalline particles. Mechanical milling of disodium cromoglycate forces larger particles to fragment, forming fairly irregular small particles varying markedly in size. Spray-dried particles, on the other hand, are almost spherical. Some partially shrunken particles are typically formed during spray-drying. The range of particle sizes in the spray-dried material

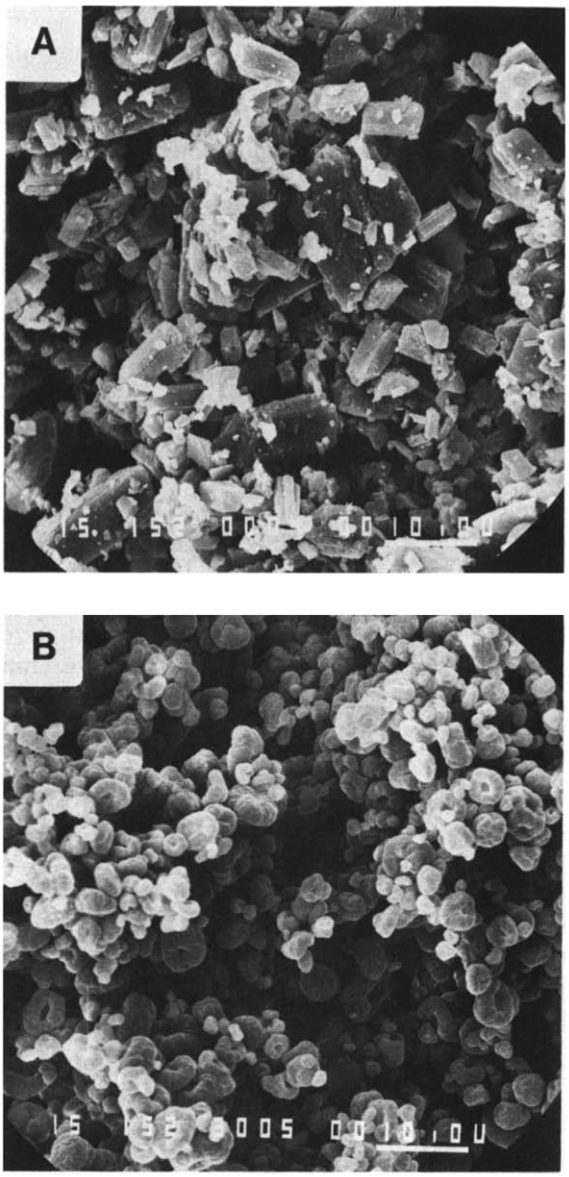

Fig. 3. Scanning electron micrographs of mechanically micronized (A) and spray-dried (B) disodium cromoglycate. Bar = 10 μm.

is also very narrow, according to the scanning electron micrographs.

Although the particles in the spray-dried sodium cromoglycate were markedly smaller than those in the mechanically micronized powder, the specific surface area of the spray-dried powder was markedly smaller than that of the mechanically

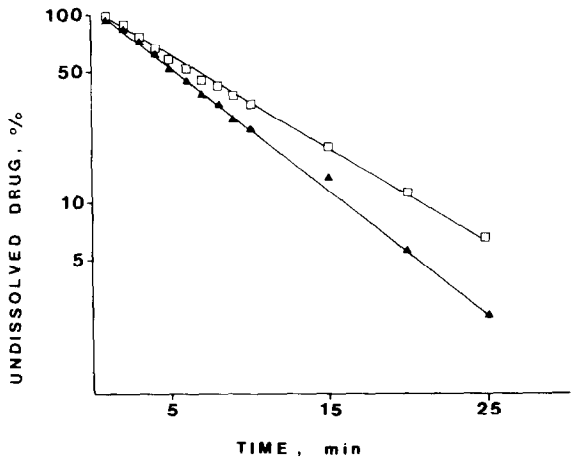

Fig. 4. Undissolved amounts of mechanically micronized (□) and spray-dried (▲) disodium cromoglycate as a function of time.

micronized powder. The reason for the difference must be the fairly irregular shape of the mechanically micronized particles. The shape factor values in Table 1 confirm this. Thus fewer contact points may exist between spray-dried particles than between mechanically micronized particles. On the basis of the results reported here it would seem reasonable to suppose that spray-dried disodium cromoglycate is less cohesive than mechanically micronized material.

Dissolution properties

From the curves in Fig. 4, it is evident that spray-drying slightly accelerates dissolution of disodium cromoglycate in phosphate buffer solution. The first-order dissolution rate constant was 0.111 $\pm$0.009 l/min for the spray-dried material and 0.142 $\pm$ 0.009 l/min for the mechanically micronized drug. This difference may result from the looser binding of the molecules in the amorphous crystal structure of the spray-dried disodium cromoglycate as compared with the fairly crystalline structure of the mechanically micronized disodium cromoglycate. Another possible reason for the difference is that the mechanically micronized drug, which is fairly cohesive, aggregates to form larger units, reducing the surface area available. On the basis of the dissolution results, use of spray-dried disodium cromoglycate in inhalation therapy would not be disadvantageous.

TABLE 2

Percentages of disodium cromoglycate particles ($\pm$ S.E.) reaching and remaining in the various stages during the in vitro inhalation test

Particle size fraction (μm)	Spray-dried material	Mechanically micronized material
> 7.1	60.6 $\pm$ 2.1	60.2 $\pm$ 4.3
3.3–7.1	13.0 $\pm$ 0.7	29.7 $\pm$ 1.5
0.3–3.3	26.4 $\pm$ 2.5	10.1 $\pm$ 0.2

Inhalation behaviour

The results obtained in the in vitro inhalation tests are shown in Table 2. Using both types of disodium cromoglycate powder, high percentages of the drug/lactose mixtures could be achieved in the simulated alveoli of less than 7 μm in size, which are regarded as therapeutically significant. On considering alveoli below 3.3 μm in size, marked differences between the spray-dried and the mechanically micronized disodium cromoglycate are evident. Spray-dried particles seem to be able to free themselves from the large lactose carrier particles at least as easily as the mechanically micronized particles.

On the basis of the results of this study, it would seem possible to use spray-dried disodium cromoglycate in inhalation therapy. The dissolution and inhalation behaviour of this material may even be more advantageous than that of mechanically micronized disodium cromoglycate.

Acknowledgements

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