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Morphic features of solid particles after micronization in the fluid energy mill

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Summary

Salbutamol particles were comminuted in a fluid energy mill to particles less than 5 μm. Fourier descriptors extracted from the particle contour clearly indicate that the shape mix of salbutamol particles, changed significantly after micronization. The resulting daughter fragments became more and more simple in shape. The study of the shape features of the original and micronized particles indicate that microgrinding results in particles with smoother boundaries, less elongation and higher degree of roundness.

Introduction

Micronization is used to reduce the particle size of active ingredients that require a very small particle size to assure both maximum surface area for solubilization and bioavailability. The principal mechanism for accomplishing size reduction is impact and attrition produced by a high velocity stream of air in the fluid energy mill (Lantz, 1982). The process appears to depend on the number of particle collision, the probability of breakage on collision and whether attrition or impact is the principal mechanism of size reduction (Perry, 1963). The design and performance of fluid energy mills are described elsewhere (Perm, 1984; Austin, 1984).

Although micronization has been used successfully in the development of suitable pharmaceutical suspension and aerosol formulations, as yet the control variables associated with microgrinding are still not fully understood.

Because size reduction is involved in the preparation of many drugs and excipients, there is a concern .today, not only with the conditions at which fracture occurs but also the shape characteristics of the set of fragments resulting from size reduction. In a recent communication from our laboratory, it was found that the morphological characteristics of talc powder can significantly affect the physical behavior of this excipient as an opicifier (Laurin et al., 1986). There is no quantitative experimental data, to our knowledge, showing the effect of micronization on the shape of solid particles. In this study, we evaluate the change in the morphological parameters of salbutamol solid particles as a result of jet grinding.

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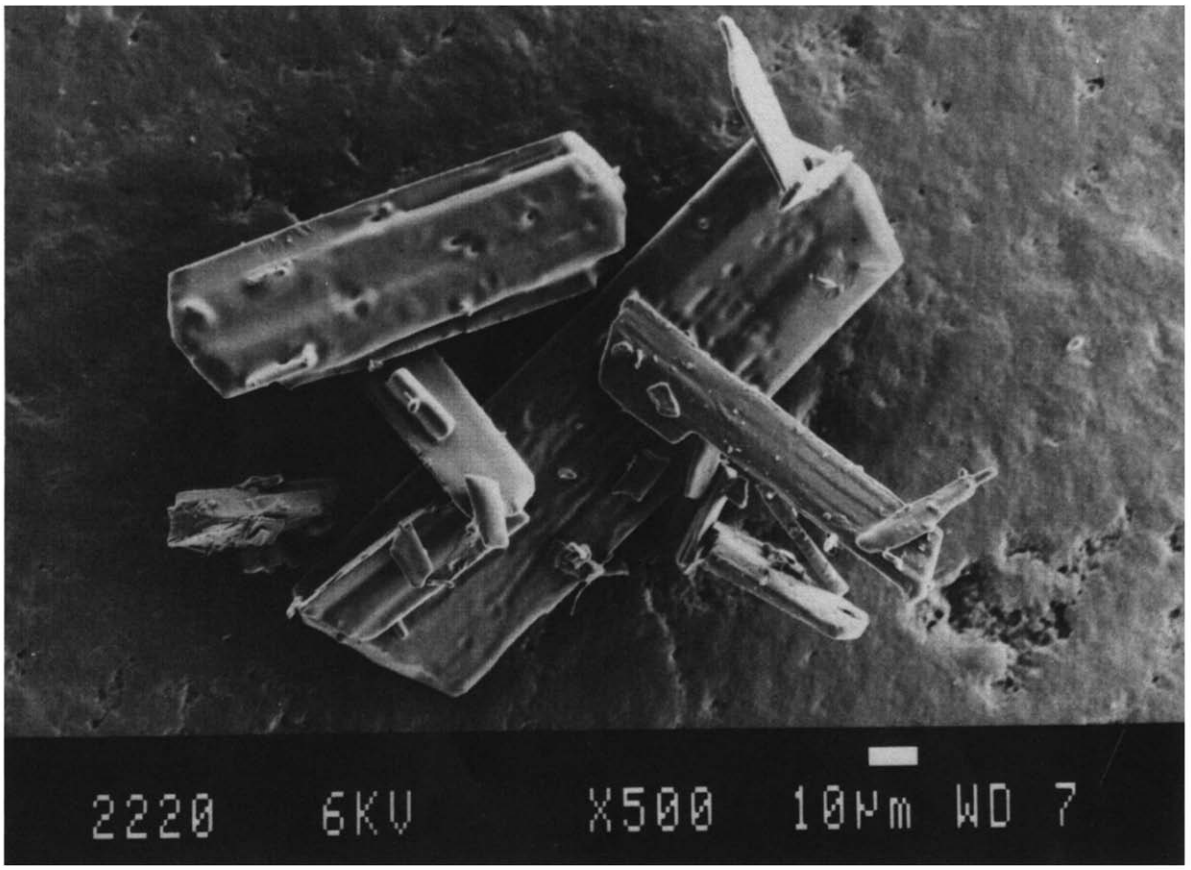

Fig. 1. Scanning electron micrograph of salbutamol crystals before micronization.

Experimental

Salbutamol base (B.P.), a crystalline powder, used as a bronchodilator was selected as a model in this study. Size reduction was conducted in a fluid energy mill [1] to a particle size below 5 μm. A series of scanning electron micrographs [2] were prepared for the original crystals, and for those obtained after micronization. These micrographs were used for the study of the size and morphological characteristics.

Size–shape determination

Size–shape analysis was determined using an image analysis system previously described (Nguyen et al., 1983; Laurin, 1985; Laurin et al., 1986). The use of Fourier descriptors is based on the digitalization of the particle image by obtaining (x, y) coordinates of the particle boundary. These coordinates are used to calculate a set of invariant shape descriptors (Beddow and Meloy, 1980).

In this method, the (x, y) coordinates of the particle boundary are represented in complex form as:

$$u(l) = x(l) + i \cdot y(l) \tag{1}$$

(Granlund, 1972) and are calculated in terms of Fourier series as:

$$u(l) = \sum_{n=-p}^{p} C_n \, e^{i 2\pi n l / L} \tag{2}$$

[1] Glaxo, Toronto, Ont., Canada.
[2] SEM-Jeol, ISM 840, Jeol, Tokyo, Japan.

where

$$C_n = \frac{1}{L}\int_0^L u(l)\, e^{-i2\pi nl/L}\, dl \qquad (3)$$

C_n = the n^{th} Fourier coefficient; n = harmonic number; l = the path length along the particle boundary; L = the perimeter of the particle; i = the complex value equal $\sqrt{-1}$; p = maximum harmonic number considered.

To obtain magnification invariance, we compute the Fourier coefficients normalized by the amplitude of the first coefficient.

$$a_n = C_n/(|C_l| + |C_{-l}|) \qquad (4)$$

Thus, the normalized amplitude of each coefficient is $|a_n| + |a_{-n}|$

Shape features characterizing the particle such as roundness, elongation, boundary variation, were also determined. These shape features were computed using Fourier coefficients, and they have the desired invariant properties (Chen and Shi, 1981). Those features are used for identification, recognition or classification.

Roundness. P_1, for example, was determined from the normalized Fourier coefficients using the following expression:

$$P_1 \frac{|a_1|}{\sum_{n=1}^{p} (|a_n| + |a_{-n}|)} \qquad (5)$$

P_1 is invariant under translation, rotation, scaling and starting point. Moreover, $P_1 = 1$ when C is a

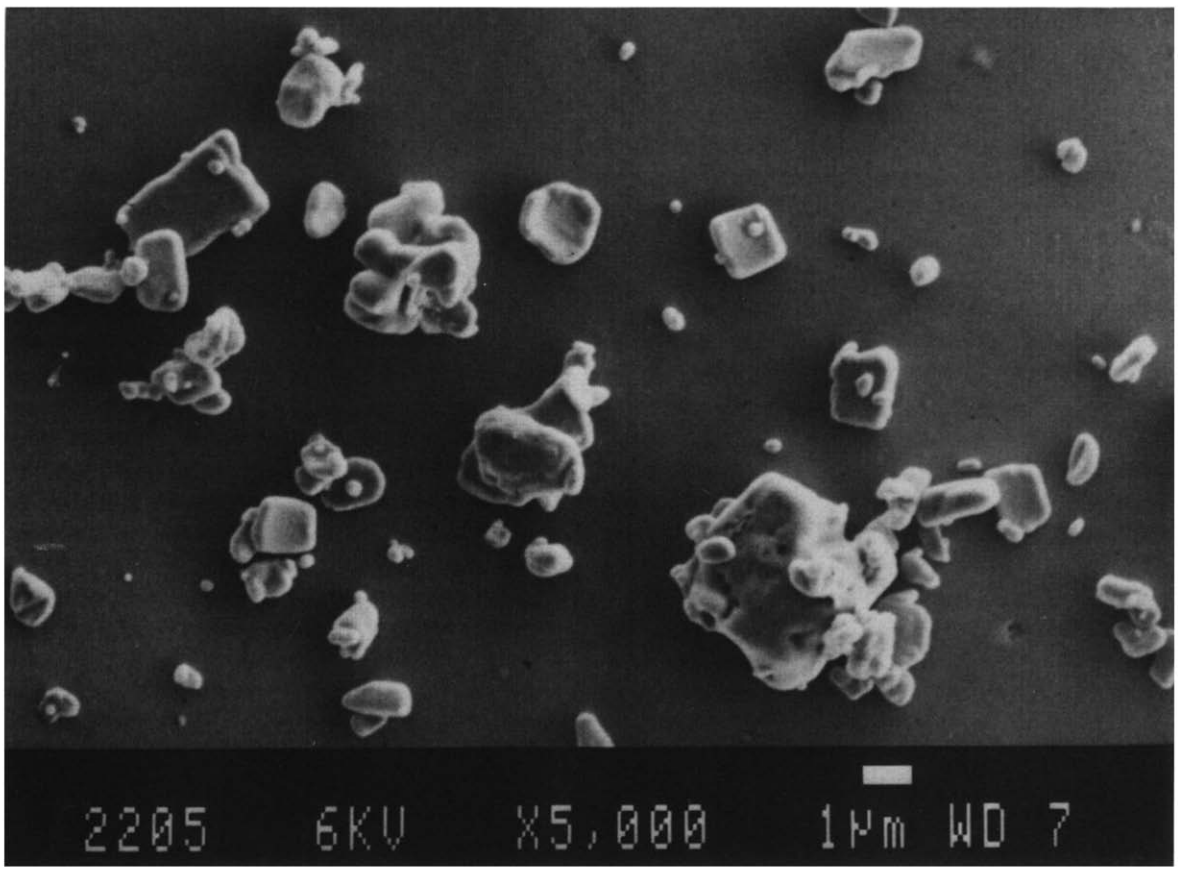

Fig. 2. Scanning electron micrograph of salbutamol crystals after micronization.

circle and $0 < P_1 < 1$ otherwise.

Elongation. P_2 was determined from:

$$P_2 = \frac{||a_1| - |a_{-1}||}{|a_1| + |a_{-1}|} \tag{6}$$

where P_2 is a measure of elongation and it gives the ratio between the major and the minor axis of the fitted ellipse. P_2 lies between 0 and 1 with $P_2 = 1$ if the contour is a circle. P_2 gets smaller as the contour becomes more elongated.

Boundary variation. (P_3)

$$P_3 = \sum_{n=m}^{p} |a_n|^2 + |a_{-n}|^2 \tag{7}$$

P_3 measures the boundary variations in part of the frequency spectrum; p is the upper limit to the spectrum at which the spectrum remains meaningful.

Results and Discussion

Micronization of salbutamol crystals took place as a result of the acceleration of the solid particles in a jet of gas, and the collision of the particles with each other. Both impact and attrition are responsible for the fragmentation and the disintegration of the original particles. Figs. 1 and 2 show the original salbutamol crystals before and after micronization. It appears clearly from SEM micrographs that the particle shape changed significantly during the process of size reduction.

HARMONIC	SALBUTAMOL AMPLITUDE	SALBUTAMOL VARIANCE	SALBUTAMOL MICRONISED AMPLITUDE	SALBUTAMOL MICRONISED VARIANCE
2	0.06957770	4.064813E-03	0.06072317	7.577263E-04
3	0.09712833	4.170272E-04	0.07008526	4.008435E-04
4	0.03275702	3.752202E-04	0.02856084	1.602737E-04
5	0.03288210	1.362739E-04	0.01930477	6.561803E-05
6	0.01968548	1.493660E-04	0.01435205	3.341244E-05
7	0.01724601	6.441664E-05	0.01123568	2.186470E-05
8	0.01461971	7.217333E-05	0.00912656	2.555007E-05
9	0.01194034	4.875244E-05	0.00891447	2.591047E-05
10	0.01122800	4.968334E-05	0.00803195	1.796496E-05

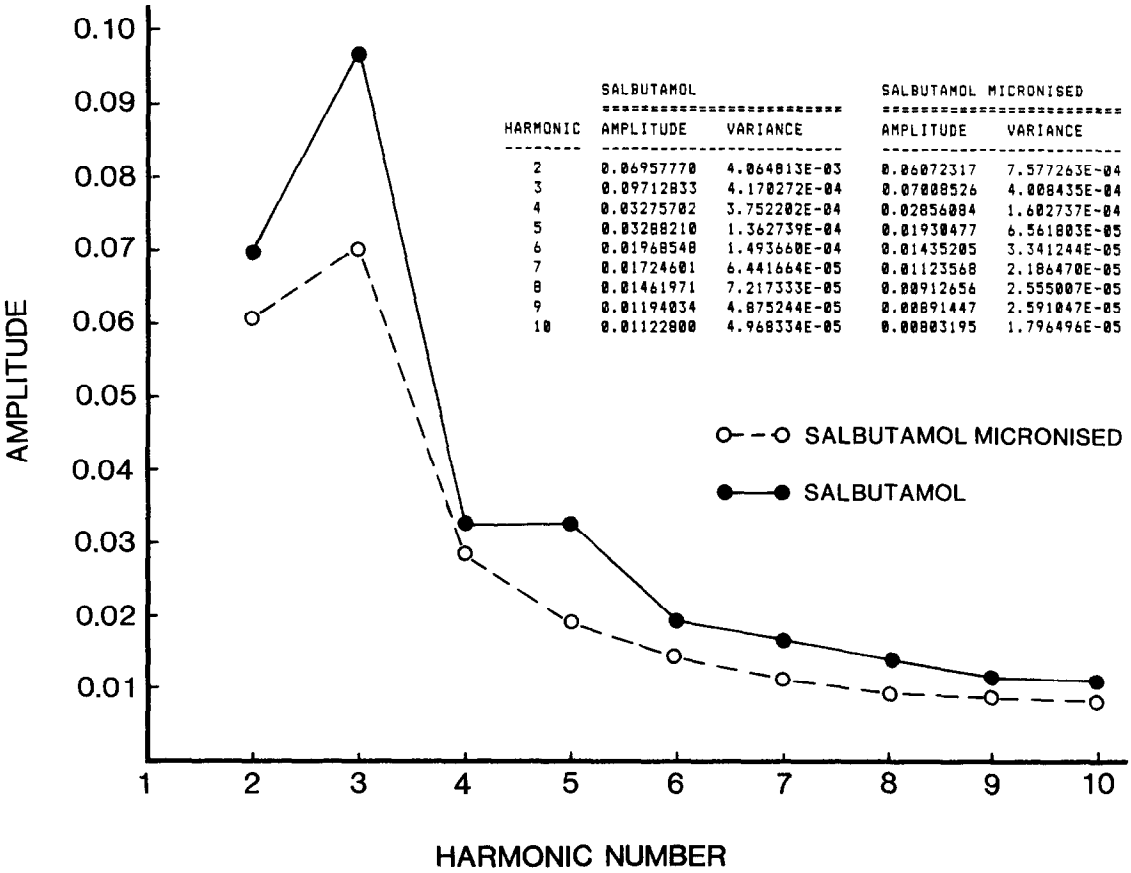

Fig. 3. Amplitude spectra. The amplitude vs harmonic number for salbutamol crystals before and after micronization.

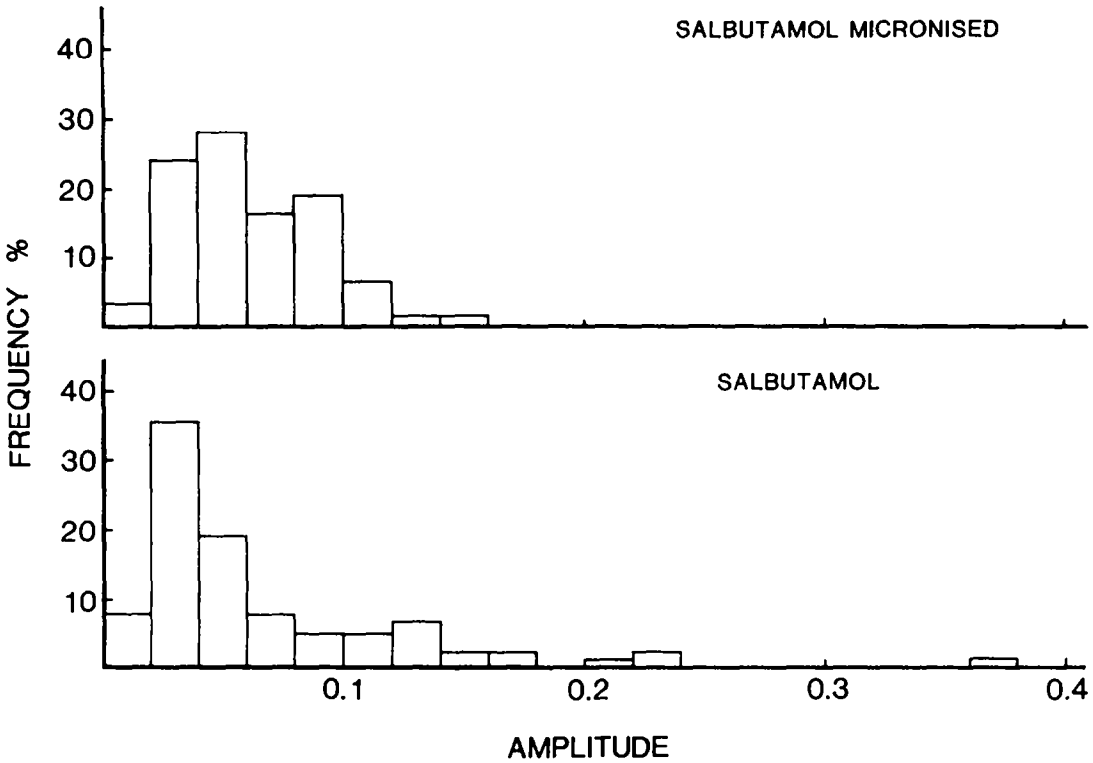

Fig. 4. Shape frequency distribution of salbutamol before and after micronization at harmonic number 2.

Large particles lost their corners and edges. The daughter fragments tend to be more round and smoother.

To quantify this phenomenon we used Fourier harmonic analysis. Fig. 3 show the morphological difference between the two salbutamol powders using Fourier descriptors. The particle signature of both powders indicates clearly how particle shape is sensitive to size reduction, and the average normalized Fourier amplitudes are lower in the micronized salbutamol. Figs. 4 and 5 show the shape frequency distribution of the two powders. At harmonic number 2 and number 5, the micronized powder consists of particles more round and less of multi modal shape than the starting material.

The shape features of the micronized and starting material is summarized in Table 1. Roundness for example is clearly show in Fig. 6 where the frequency distribution of roundness for the two powders is given. The examination of the distribution curves shows that the roundness P_1 of the micronized particles appears to move towards a higher value (where 1 corresponds to a circle). Fig. 7 shows the frequency distribution of elongation P_2. Since elongation P_2 is a measure of the ratio between the major axis and the minor axis of the fitted ellipse, the increase in P_2 means that the micronized particles are less elongated. Similarly, the study of the boundary variation P_3 (Fig. 8)

TABLE 1

Shape parameters of salbutamol crystals before and after micronization

Size shape parameters	Salbutamol	Salbutamol micronized
Diameter (μm)	43.95	1.44
Roundness	0.51	0.63
Elongation	0.44	0.69
Boundary variation	1.66	0.07

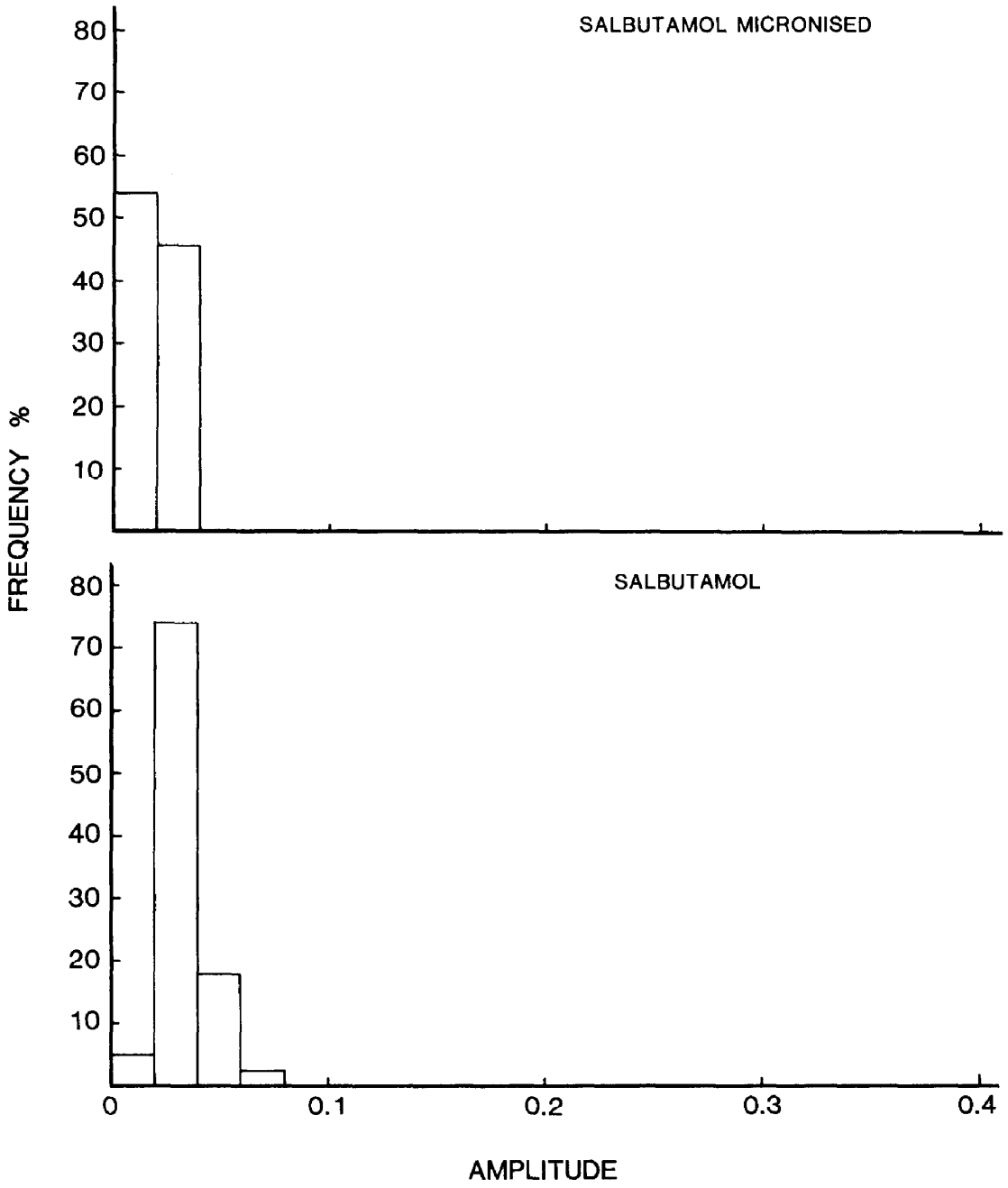

Fig. 5. Shape frequency distribution of salbutamol before and after micronization at harmonic number 5.

indicates that micronization produced particles with smoother boundaries, and P_3 of the micronized salbutamol is closer to 0 than the starting material.

The cohesiveness of very fine powders (like micronized salbutamol) has not been treated in the literature either theoretically or experimentally, although it is frequently the source of a

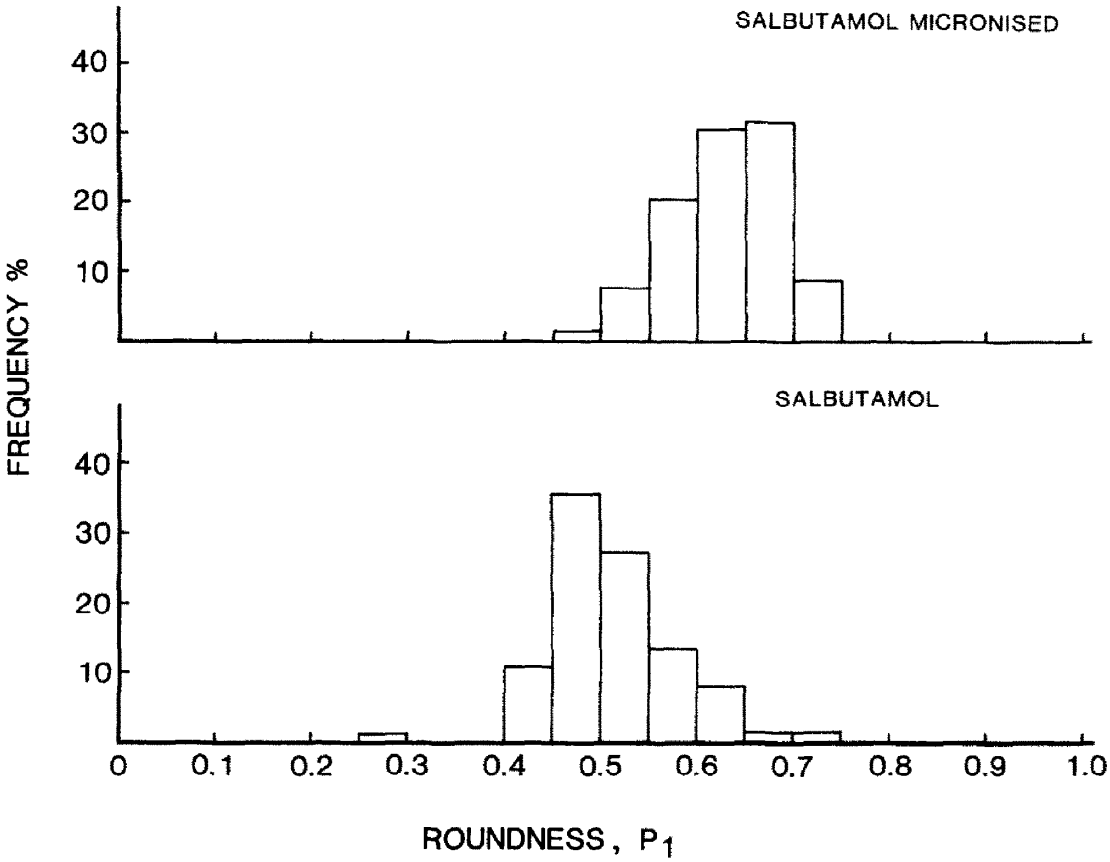

Fig. 6. Roundness frequency distribution of salbutamol crystals before and after micronization.

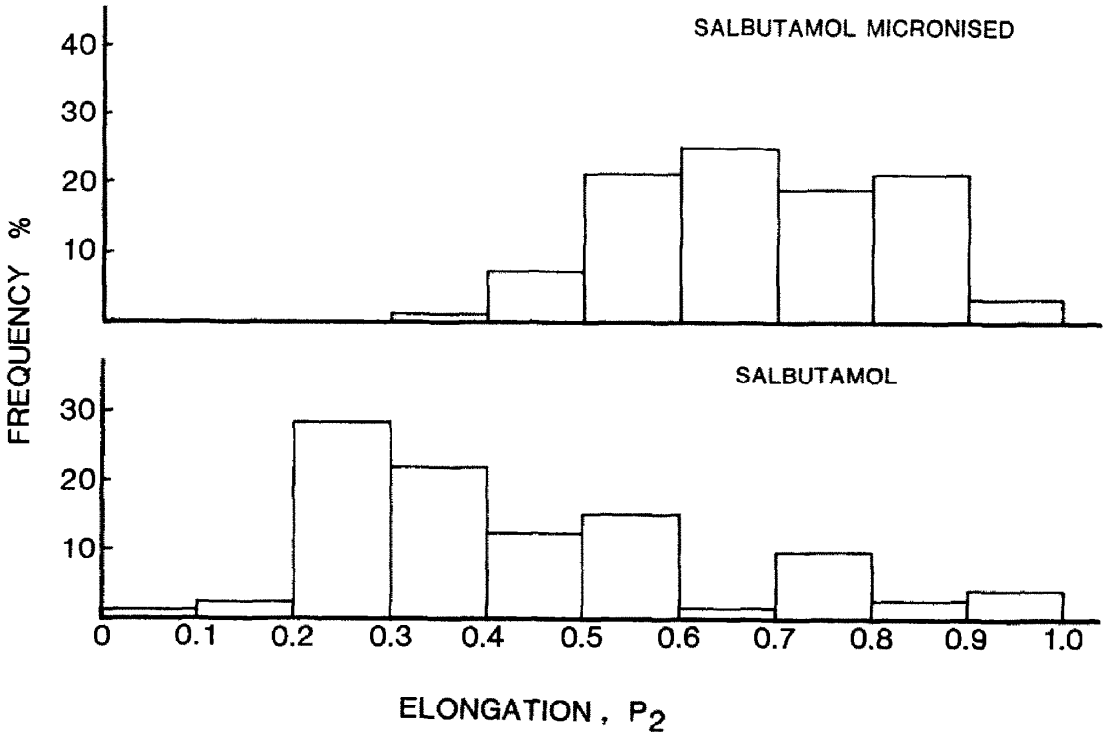

Fig. 7. Elongation frequency distribution of salbutamol crystals before and after micronization.

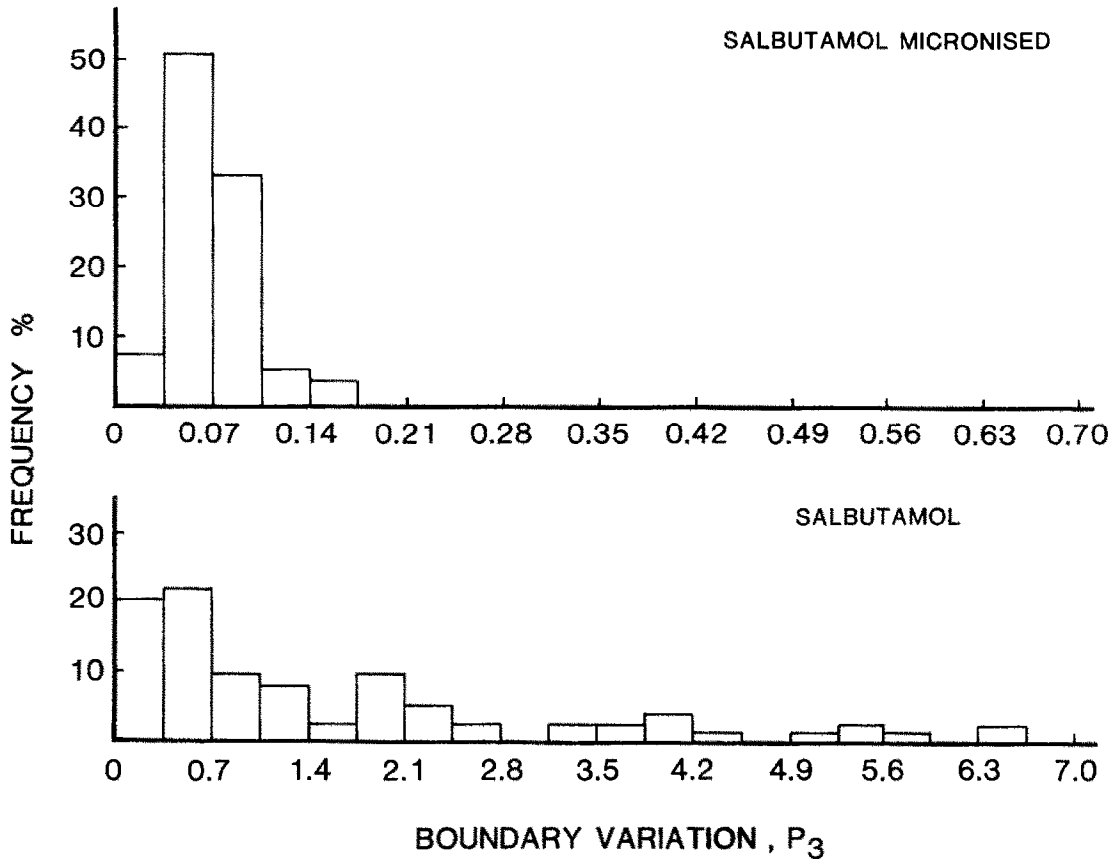

Fig. 8. The frequency distribution of boundary variation of salbutamol crystals before and after micronization.

number of substantial problems in the manufacture and application of such materials in aerosol preparations. It is believed that this new tool in the study of shape features could be of significant value in the validation of the size reduction techniques used in the pharmaceutical industry to produce particulate systems with the desired functional properties.

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