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Short Communications

Properties and dissolution of drugs micronized by crystallization from supercritical gases *

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Jet milling is a usual method for micronization of drugs to enhance their surface areas. Recently Glatz (1985) reported that very fine particles of steroids are produced by expanding the solution of the drug in a supercritical gas. If the substance tends to any instability reaction, the micronization requires mild conditions which are met by recrystallization from supercritical gases, as aprotic solvents and relatively low temperatures (40–80 °C) are used.

For the investigations described below phenacetin, as an example, was micronized by jet milling as well as by expanding solutions of the substance in supercritical carbon dioxide or trifluoromethane. Phenacetin powders produced in these different ways show identical melting points, DSC diagrams and densities, indicating the absence of polymorphic forms. However, the materials differ in their particle forms, specific surface areas and, immediately after the micronizing, in their contact angles; after some days the contact angles approached corresponding values (Table 1). All these substances are electrostatic charged.

The Fisher subsieve sizer (permeability measurement) and the Cilas-Granulometer 715 (laser light diffraction) were used to evaluate the surface areas. Calculations were done on the basis of the log-normal distribution assuming a spherical form of the particles. The values of the surface areas measured by both methods are in fair accordance for the phenacetin powder obtained by jet milling (Table 1), but differ considerably for the powders produced by crystallization from supercritical gases. In these cases the permeability method yields much higher values than the laser light diffraction measurements. The differences result from the real particle form. As can be seen from the Fig. 1a–c, particles obtained from compressed gases are crystal skeletons, formed with great velocity during the gas expansion. They build up a network-like powder bed by connecting particles through solid bridges. On the other hand the jet-milled particles are compact and nearly spherical.

From that knowledge interest in dissolution rate of these powders arises. The dissolution measurements are evaluated by means of the Weibull function in the logarithmic form in which $1/t' = k_w$ has the meaning of a dissolution rate coefficient (Loth and Schäfer, 1985):

* Dedicated to Professor Dr. Peter Speiser on the occasion of his 65th birthday.

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TABLE 1

SURFACE AREAS, CONTACT ANGLES AND MELTING POINTS OF DIVERSELY MICRONIZED PHENACETIN POWDERS

	Phenacetin micronized by:		
	Jet milling	Expanding of supercritical	
		Carbon dioxide	Trifluoromethane
Melting point (°C)	136.5	136	136.5
Contact angle			
on the day of micronizing (°)	87.6	89.5	83.2
10 days after micronizing (°)	77.5	78	77.5
Surface area			
Fisher subsieve sizer (cm^{-1})	14,500	23,800	34,100
granulometer (cm^{-1})	11,900	14,800	16,400

$$\log \log\left(\frac{m_u^0}{m_u^0 - m_u}\right) = n \log\frac{1}{t'} + n \log(t - t_L) - 0.362$$

$$= n \log k_w + n \log(t - t_L) - 0.362 \qquad (1)$$

where m_u = mass of undissolved drug at time t; m_u^0 = undissolved mass at time t = 0, equals entire mass of powder; t' = time, after which 63.2% of m_u^0 have dissolved; t_L = experimental lag time; n = coefficient of the Weibull function.

In spite of the considerable differences in the surface areas, the dissolution rate coefficients of the three pure micronized phenacetin powders have nearly the same values (Table 2). This shows the big influence of agglomeration and of wetting because phenacetin is not a readily wetted substance. Mixing with hydrophilic vehicles can diminish the agglomeration of the drug particles and improve the wetting. Admixture of 1% Aerosil R 972 increases the dissolution rate constants about 3- to 5-fold. Much higher values (25- to 32-fold) were obtained if phenacetin is mixed one-to-one with mannitol or with a blend of mannitol and Aerosil R 972 (99 + 1). In these cases phenacetin micronized by supercritical trifluoromethane dissolves most quickly. In comparison to the jet-milled drug, the powders produced by crystallization from supercritical gases have greater surface areas; therefore it seems possible to accelerate the dissolution of these phenacetin powders further on using suitable vehicles and manufacturing methods; additional investigation is in progress.

TABLE 2

DISSOLUTION RATE COEFFICIENTS OF MICRONIZED PHENACETIN PREPARATIONS

Phenacetin preparations	Dissolution rate coefficient $k_w = \frac{1}{t'}$ (min^{-1}) of phenacetin micronized by:		
	Jet milling	Expanding of supercritical	
		Carbon dioxide	Trifluoromethane
Pure	0.089	0.078	0.091
Mixed with			
Aerosil R 972 (99 + 1)	0.27	0.31	0.45
mannitol (1 + 1)	2.2	2.1	2.8
mannitol with 1% Aerosil R 972 (1 + 1)	2.3	2.2	2.9

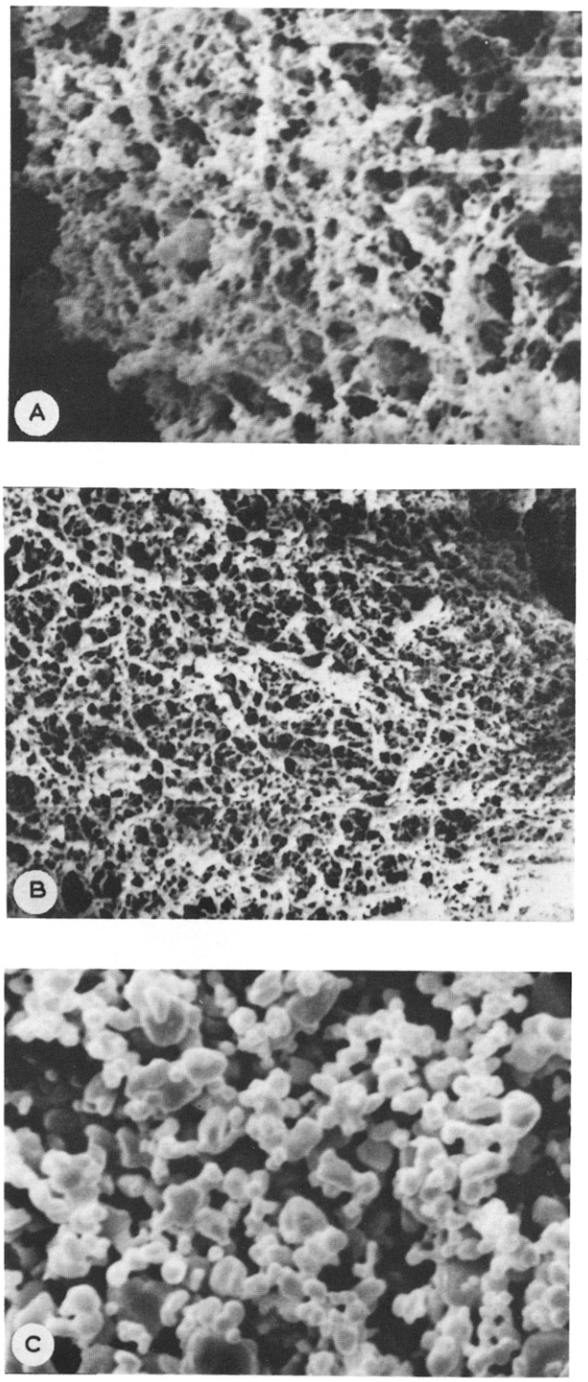

Fig. 1. Raster electron micrographs (Can-Scan; 20 kV, SE, Au-spattering) of micronized phenacetin powders. A: crystallization from supercritical trifluoromethane (4.33 mm ≙ 10 μm). B: crystallization from supercritical carbon dioxide (3.6 mm ≙ 10 μm). C: jet milling (13 mm ≙ 10 μm).

Micronization by jet milling. Chrispro-Jet-Mill MC-100 KX (Micromacinazione, CH-Molinazzo di Monteggio), air pressure: 5 bar, substance feeding; 1 g/min.

Micronization by supercritical gases. Apparatus by Stahl (Stahl et al. 1986); phenacetin is dissolved in carbon dioxide at 60°C and 600 bar or in trifluoromethane at 80°C and 500 bar. Crystallization proceeds during the expansion of the gases.

DSC. Thermal Analyzer 990 with DSC-cell 910, Du Pont de Nemours.

Contact angle. Contact-angle-meter G-1, Erma, Tokyo.

Dissolution. Hanson Dissolution Tester USP (70 rpm; 37°C) combined with a pump (Gilson Minipuls 2) and an external flow-through cell for spectrophotometric measurement (Perkin-Elmer model 551 S; 244 nm); solvent 500 ml 0.01 N HCl adjusted to a surface tension of $\sigma = 45 \pm 5$ mN · m^{-1} by Tween 80; amount of drug, 50 mg (or an equivalent amount of mixture), strewn on the solvent surface.

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