Scale up considerations in fluidized bed granulation: air flow rates and air pressure distribution

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Fluidized bed granulation is now well established as a method for the preparation of granulates for tableting. The influence of the composition and procedure adopted, on the granulate characteristics has been investigated for both batch production (Davies & Gloor, 1971, 1972, 1973) and continuous production (Scott & others, 1964; Rankell & others, 1964). Studies of the mixing, granulating and drying steps have also been undertaken (e.g. Thurn, 1970). Experiences during scale-up from laboratory to production equipment have been reported (e.g. Gupte, 1973) but no reliable scale-up procedure has been completely elucidated. In the work reported here, comparisons of the air flow rate and air pressure distribution in two fluidized bed granulators (models WSG 5 and WSG 30, Glatt, Haltingen, West Germany) are made.

By means of a Pitot tube linked to a Micromanometer (Furness Controls Limited, Bexhill-on-Sea) the effect of load (Lactose B.P.) on the air flow rate through each piece of equipment has been determined over a range of inlet and outlet air valve settings. In each case, it is shown that an increase in load (a) reduces the air flow rate through the equipment and (b) reduces the useful range of the inlet and outlet air valve settings. By comparing the air flow rates obtained in each apparatus a scale-up factor of 5 is indicated. This compares well with the factor obtained from the dimensions of the two models.

Static pressure measurements were made at three points in the WSG 5 and WSG 30; namely, beneath the distributor plate of the product container, in the expansion chamber and above the exhaust filter. For both models, the outlet valve had a greater effect on the air pressure than the inlet valve, and the pressure change across the distributor plate exceeded that across the exhaust filter. However, the maximum reduction in pressure achieved in the expansion chamber was greater for the WSG 30 than for the WSG 5 (approx. 500 and 350 mm water respectively); a fact which may result in different rates of drying on scale-up.

When loaded with lactose (5 and 30 kg in the WSG 5 and WSG 30 respectively) the pressure change across the exhaust filter of both models was followed during several shake cycles. It was found that the filter resistance increased during the period between shakes but returned to its original value immediately after shaking, i.e. the shaking is effective in removing fines from the bag.

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Particle size obtained on disintegration of phenylbutazone tablets and its relation to dissolution rate

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The biological availability of a drug in a solid dosage form depends upon the rate at which it achieves solution. The disintegration test for coated or uncoated tablets (B.P. 1973) is the only official method by which some assessment of bioavailability may be obtained. However, disintegration time has often been shown (Lowenthal, 1972) to be independent of dissolution rate, and Sandell & Helmstein (1971) have suggested replacement of the USP XVIII disintegration test with a refined procedure employing a wet sieving apparatus. This work examines the relationship between particle size after disintegration and the dissolution profiles obtained for phenylbutazone tablets from several manufacturers.

The dissolution profiles were obtained using the method of Searl & Pernarowski (1967); particle size data was obtained by wet sieving and Coulter analysis methods similar to those of Shotton & Leonard (1972).

Considerable differences were observed between batches of tablets from different manufacturers. Examination of batches with differing dissolution profiles showed no relationship between disintegration time, tablet hardness and t_{50} (time for solution of 50 mg drug).

The median particle diameter obtained after the disintegration test was inversely related to the dissolution rate expressed as t_{50}. It was also possible to relate dissolution rate to surface area of particles in the subsieve range. The size rather than total amount of particles in the subsieve range was shown to be important since there was no correlation between dissolution rate and percent total tablet weight passing through the sieves.

Comparison of tablets from the same manufacturing batch indicated that coating delayed initial disintegration but had only a small effect on subsequent disaggregation, indicating that in this instance shellacing has minimal effect on tablet breakup.

Dissolution rate of phenylbutazone tablets therefore appears to be dependent on the degree of disaggregation, rather than disintegration time.

The results are summarised in Table 1.

Table 1.

Tablet batch	disintegration time (min)	t_{50} (min)	Mean particle diameter after disintegration test (μm)	Subsieve range		Mean tablet hardness
				Surface area ($cm^2\ cm^{-3}$)	% Total tab wt	
A	3·2	34	280	2962	7·05	3·4
B	11·5	51	330	3112	1·97	6·3
C	>15	231	900	1725	1·54	4·3
D	>15	393	1350	1764	1·74	4·8
E	6·4	158	520	2664	5·54	3·2
F*	25	197	620	2850	—	—

* F comprises sugar coated tablets from the same manufacturing batch as uncoated tablets E All other batches are uncoated.

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Size analysis of sub-micron particles by centrifugal photosedimentometer

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A new centrifugal photosedimentometer is described which uses light carried from a helium-neon laser to silicon photodiodes with optical fibres. The photo-detectors are set beneath a transparent centrifuge tank containing a dilute homogeneous suspension of the material under examination and in this manner a continuous series of measurements of the optical density of the sedimenting systems can be obtained as a function of time without the need for the electro-mechanical servo-systems which have been a feature of previous designs (Groves & Freshwater, 1968). The intense monochromatic character of the laser light has improved the sensitivity of the method and particles corresponding to a Stokes' diameter of 0·018 μm have been detected in a sample of a commercial intravenous emulsion.

The relation between the cross-sectional area of the particles obscuring the light beam and the observed optical density at a given time is complex owing to diffraction effects as the diameter of the particles approach the wavelength of the incident light. However, in