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Ordered Mixing in Direct Compression of Tablets

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SUMMARY

The mixing of 2% sulphaphenazole (mean diameter 25 μm) with coarse directly compressible tablet vehicles has been studied using a sampling method and scanning electron microscopy. At a certain vehicle particle size, sulphaphenazole appears to mix by an ordered process. After mixing with a 180 - 250-μm size fraction of a sucrose-based vehicle (Dipac) for 100 minutes, the standard deviation of sulphaphenazole content of 200-mg samples was equivalent to that predicted for a random mix. The mix did not appear to segregate during mixing or on vibration. Under scanning electron microscopy in conjunction with energy dispersive analysis of X-rays, sulphaphenazole appeared to be distributed quite uniformly on the coarse vehicle particles.

INTRODUCTION

The advantages of direct compression of tablets over traditional granulation techniques have been well documented [1 - 3]. In its simplest form the process involves just one unit operation, that of mixing of drug and vehicle, prior to compression. The technique is probably most suitable for microdose tablets where the drug represents less than 5% of the total mix. From a drug dissolution standpoint the drug should be present in as fine a particle size as possible, whereas to ensure flowability the vehicle should be in a coarse granular form. This poses a mixing problem. Classical random mixing theory states that such a system would be difficult to mix.

Recently, the concept of ordered mixing has been introduced [4]. This arose from an awareness that many glidants and lubricants act by adhering onto larger particles, improving flow [5 - 7]. If by careful selection of drug and vehicle particle size a non-segregating ordered system could be constructed, direct compression could be a useful method of presenting small amounts of relatively insoluble drugs in a homogeneous form. The extragranular position of the drug should ensure high dissolution rates.

In this work the mixing of a fine drug, sulphaphenazole, with various size fractions of two commercially available direct compression tablet vehicles was studied. Sulphaphenazole was selected as it has a cohesiveness and particle size distribution similar to drugs which are used in low dosage, *e.g.* digoxin, steroids.

MATERIALS AND METHODS

Sulphaphenazole was kindly donated by Ciba-Geigy Australia. Using an Alpine air-jet sieve, the particle size distribution was found to be log-normal. The geometric mean weight diameter (d_{gw}) is 25 μm and the geometric standard deviation (σ_g) is 1.50. Celutab is a dextrose–maltose vehicle obtained from Brown and Dureau. From sieve analysis using an Endecott sieve shaker, d_{gw} was estimated as 325 μm with a σ_g value of 1.75. Dipac, obtained from Amstar Corporation, is a sucrose–dextrin vehicle with a d_{gw} of 255 μm and σ_g of 1.28. By liquid displacement studies at 25 °C, particle densities of sulphaphenazole, Celutab and Dipac were estimated as 1.06, 1.41 and 1.52 g ml^{-1} respectively.

Mixing was carried out in an Erweka stainless steel cube mixer (capacity 8 l) rotating at 20 rpm. The initial load was 800 g, and at various time intervals 20 × 200-mg samples were removed using a sample thief. The samples were assayed by dissolution in 40 ml of

0.5% sodium carbonate and absorbance measurement at 250 nm using a Varian 635 u.v. spectrophotometer.

After 100 minutes some systems were examined under a JSM-U3 scanning electron microscope (JEOL Co. Ltd.) fitted with a device for energy dispersive analysis of X-rays (EDAX — Nuclear-Diodes Inc.).

DEGREE OF MIXEDNESS

In the selection of a mixer and the required mixing time, it is necessary to compare a measure of the variation of drug content in the mix (normally the standard deviation) with various parameters.

The most common parameter used is the standard deviation for the fully randomised mix, σ_R. Lacey [8] showed that the standard deviation of a fully randomised two-component system of identical densities and particle size was given by

$$\sigma_R^2 = xy/N \quad (1)$$

where x and y are the proportions of the two components and N is the number of particles in the sample taken. For a mix of two components, N is given by [3]

$$N = \frac{6W}{\pi}\left(\frac{x}{(d_{vn})_x^3 \rho_x} + \frac{y}{(d_{vn})_y^3 \rho_y}\right) \quad (2)$$

where W is the weight of the sample and d_{vn} and ρ are the volume-number mean diameter and density respectively of each component.

The value of σ_R in a directly compressible system where components are of differing size is probably of limited absolute significance, particularly if ordered rather than random mixing occurs. However, it can be of value in selection of particle size of drug.

Where σ_R is small, representing less than 2% of the mean, the standard deviation of the sampling and analytical procedures (σ_S) cannot be ignored. Thus the lowest standard deviation that could be achieved for the idealised system as described by Lacey would be σ_E, where

$$\sigma_E = \sigma_R + \sigma_S \quad (3)$$

A more useful value in the practical situation is the standard deviation necessary to comply with pharmacopoeial specifications or a manufacturer's own specification, σ_A [9]. In this work, σ_A was estimated for 95% of samples falling within ±10% of the mean, x, then

$$\pm 1.96\sigma_A = \pm 0.10x \quad (4)$$

or $\sigma_A = 0.05x$. Thus if the mean drug content of a 200-mg sample is 4 mg, σ_A would be equal to 0.20 mg.

RESULTS AND DISCUSSION

Figure 1 shows the change in standard deviation with time of a mix of 2% sulphaphenazole in Celutab. Studies were carried out with various size fractions of Celutab in addition to the unsifted material. Values of σ_R, σ_E and σ_A are included on the ordinate. As the number of sulphaphenazole particles per 200-mg sample greatly exceeds the number of Celutab particles, σ_R is relatively independent of Celutab particle size. Mixing with the unsifted Celutab is very poor. After rapid initial mixing the system segregates, and after 30 min the standard deviation of sulphaphenazole content is greater than 1 mg. Segregation also occurs in the 250 - 355-μm and the 355 - 500-μm Celutab, and to a lesser extent with the 180 - 250-μm fraction. Using these size fractions of Celutab it was not possible to mix within a manufacturer's specification of σ_A equal to 0.2 mg in 100 min.

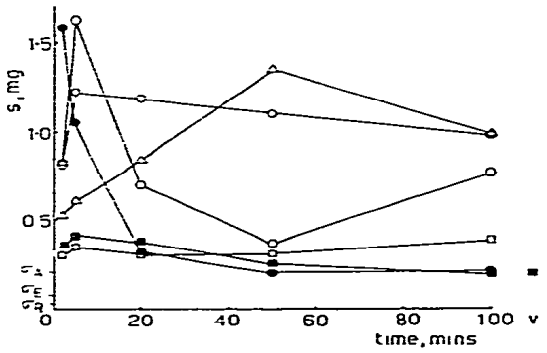

Fig. 1. Plot of standard deviation of sulphaphenazole content of 20 × 200-mg samples *vs.* time for mixing of 2% sulphaphenazole with Celutab — Unsifted, ○; 180 - 250-μm, □; 250 - 355-μm, △; 355 - 500-μm, ○; 500 - 710-μm, ●; 710 - 1000 μm, ■. σ_R is the theoretical standard deviation of the fully randomised mix neglecting standard deviation of the sampling and analytical procedure, σ_S. σ_E is equal to the sum of σ_R and σ_S. σ_A is a typical manufacturers mixing specification as given by eqn. (4).

However, on increasing the Celutab particle size fraction to 500 - 710-μm mixing improves, and after 50 min the standard deviation of sulphaphenazole content is equivalent to σ_A. Further mixing does not occur, but the system does not appear to segregate. A similar degree of mixedness can be achieved after 100 min using the 710 - 1000-μm Celutab. After mixing, this material was vibrated in the hopper of a Manesty SP1 single-punch tablet machine for one hour. The standard deviation of samples taken from this material, indicated by "V" on Fig. 1, suggests that the mix is stable to such vibration.

Mixing of 25-μm sulphaphenazole with 710 - 1000-μm vehicle particles is undoubtedly not a random process. To further investigate the system, scanning electron microscopy was used. Sulphaphenazole particles appear to be quite angular, existing mainly as agglomerates (Fig. 2). 710 - 1000-μm Celutab particles appear to consist of 10 - 20 smaller spherical particles fused together to form an aggregate, which is stable to handling (Fig. 3a). On higher magnification the surface appears relatively porous, with few fines adhering (Fig. 3b). At even higher magnification the fine structure of the Celutab particle appears porous and angular (Fig. 3c).

After mixing for 100 min with 2% sulphaphenazole, the Celutab particle adopts a "furry" appearance possibly suggesting the presence of adsorbed fines (Fig. 4a). At magnifications corresponding to those used in

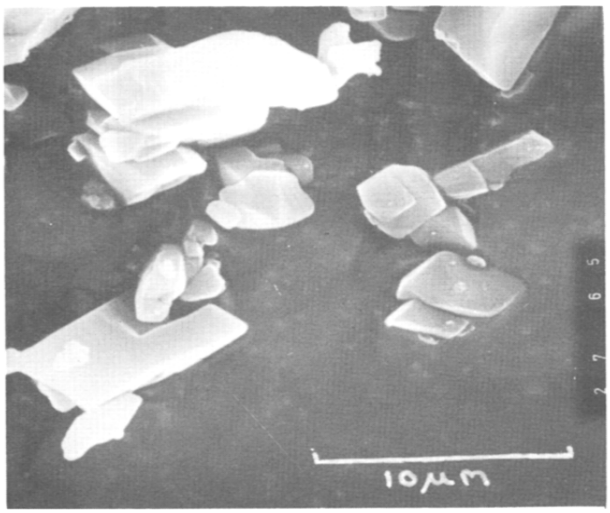

Fig. 2. Scanning electron micrograph of sulphaphenazole particles.

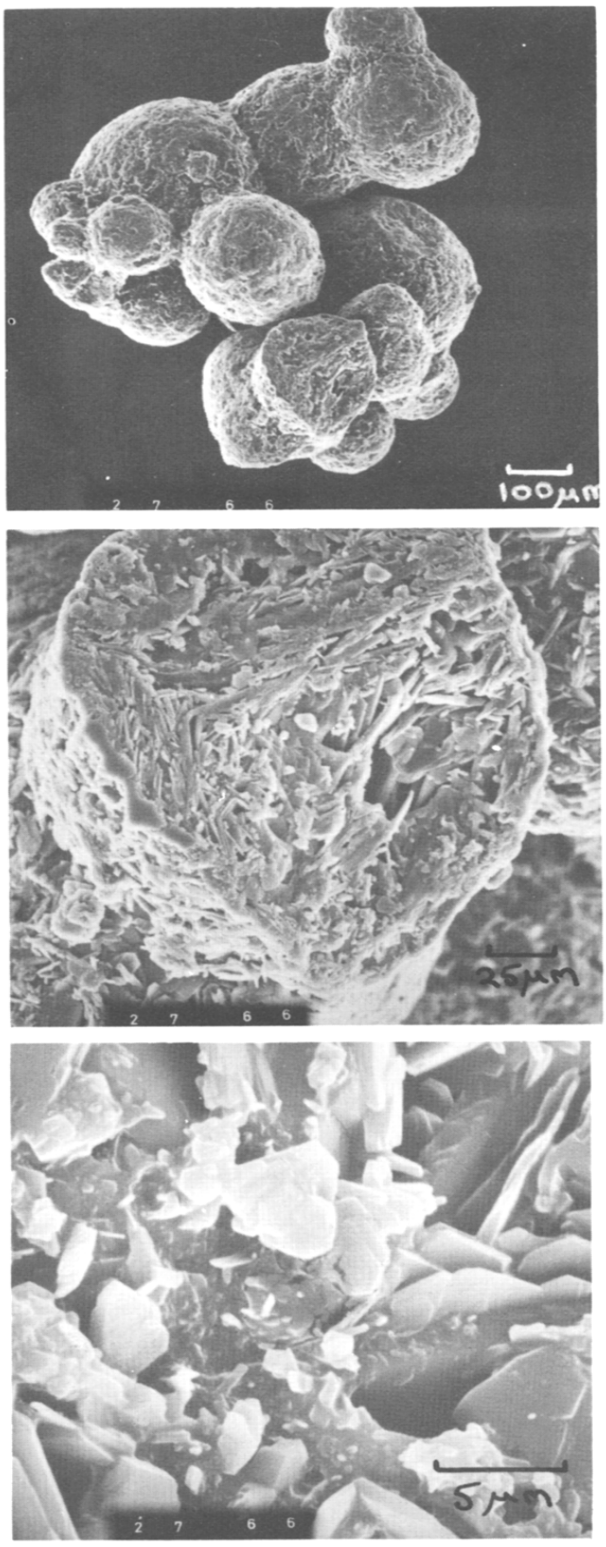

Fig. 3. Scanning electron micrographs of a Celutab particle (710 - 1000-μm sieve fraction).

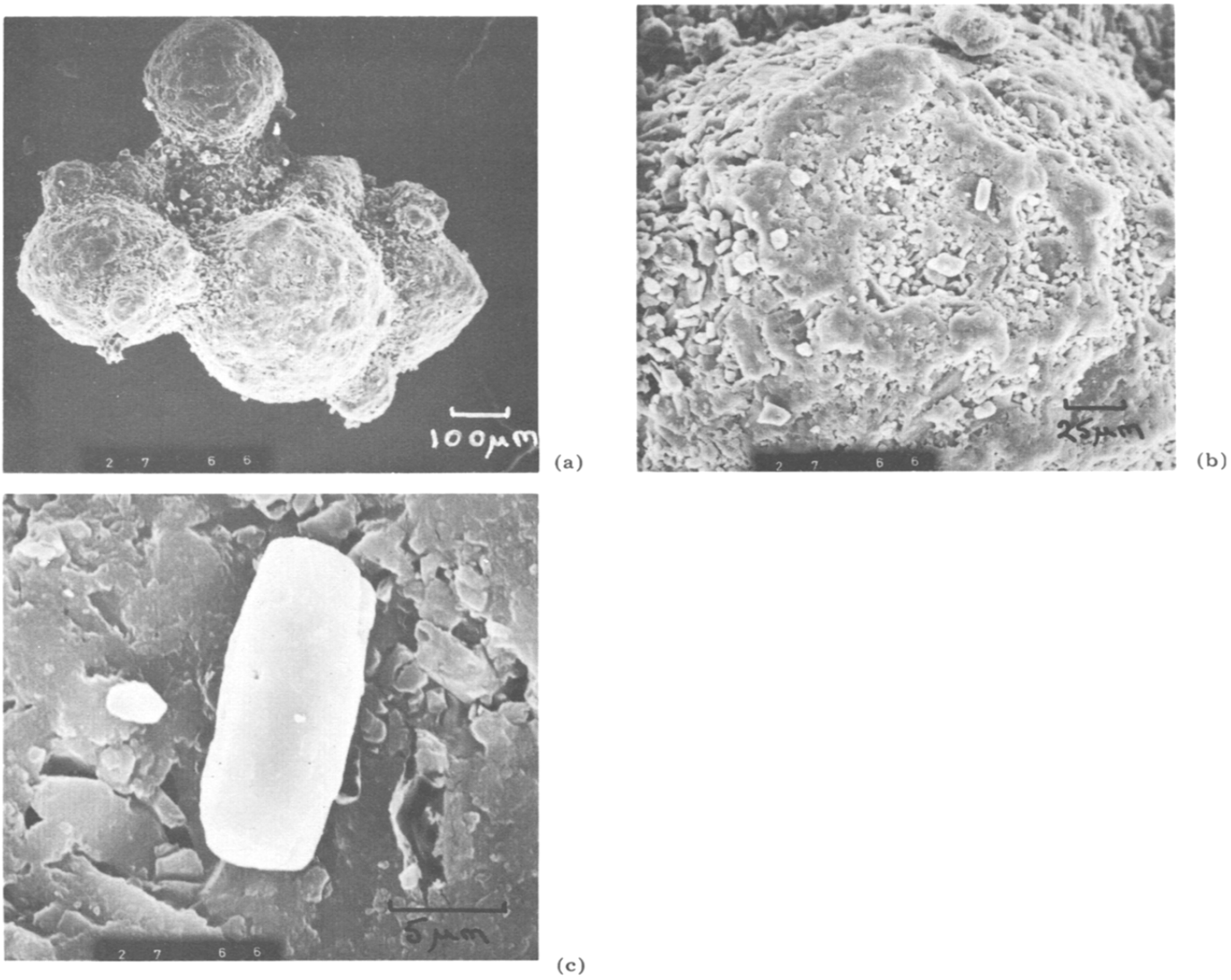

Fig. 4. Scanning electron micrographs of a 710 - 1000-μm Celutab particle after mixing for 100 min with 2% sulphaphenazole.

Fig. 3(b) and (c), adsorbed particles can be visualised (Fig. 4b, c). At 2000× magnification such a particle appears to resemble sulphaphenazole (Fig. 4c).

Using conventional scanning electron microscopy it is difficult to estimate the number of adsorbed sulphaphenazole particles per Celutab particle. For this purpose the EDAX system was used. In this mode, the X-rays emitted when the electron beam strikes the surface of the particle can be analysed to yield information as to the chemical composition of the top layer of the sample. The detector is sited close to the specimen, and energy discrimination takes place within it. The lower end of the range of a solid-state counter detector is 1 keV, so elements lighter than sodium will not be detected. Thus it is possible to scan Celutab particles for sulphur with very little background from the vehicle, consisting essentially of only hydrogen, carbon, nitrogen and oxygen. The detector was set to pick up X-rays of 2.307 keV, representing the major peak for sulphur.

Figure 5 is an EDAX photograph of a 710 - 1000-μm Celutab particle after mixing with 2% sulphaphenazole. The white spots represent 2.307 keV X-rays and the concentrated areas

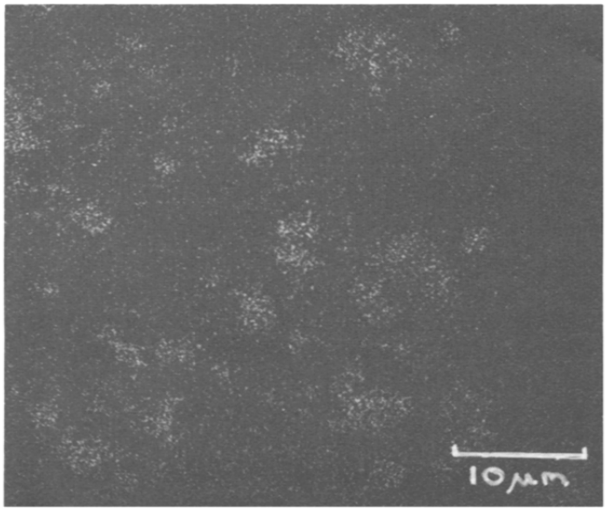

Fig. 5. Scanning electron micrograph of the system in Fig. 4 under EDAX.

of spots represent the sulphaphenazole particles. The area scanned is approximately 1/110 of the surface area of a Celutab particle. From consideration of the size distribution of the two components, there should be approximately 2140 sulphaphenazole particles per Celutab particle in the mix. From Fig. 5 there appear to be approximately 25 sulphaphenazole particles in the area scanned, representing 2750 particles per Celutab particle. This good agreement suggests that the majority of sulphaphenazole particles are adsorbed onto the vehicle particles rather than free within the mix.

Figure 6 shows mixing data of 2% sulphaphenazole in Dipac. Again, mixing with unsifted Dipac is poor, but with a 180 - 250-μm fraction the observed standard deviation was

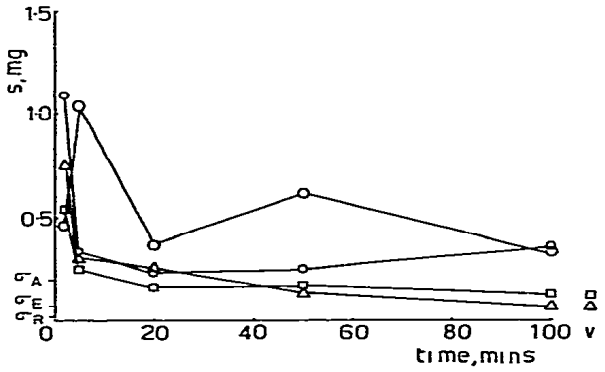

Fig. 6. Plot of standard deviation of sulphaphenazole content of 20 × 200-mg samples *vs.* time for mixing of 2% sulphaphenazole with Dipac — Unsifted, ○; 180 - 250-μm, △; 250 - 355-μm, □; 355 - 500-μm, ○.

equal to σ_E. Thus a mix was achieved which is the best possible from random mixing theory. No segregation can be observed, even after vibration for one hour in the single-punch tablet machine hopper. Figure 7(a) and (b) shows scanning electron micrographs of a 180 - 250-μm Dipac particle and Fig. 8(a) and (b) shows a similar particle after mixing with sulphaphenazole. Adsorbed drug can be identified. Under EDAX of three different Dipac particles (Fig. 9), it is easy to count the number of bound particles. Within each area scanned, there appear to be approximately 15 sulphaphenazole particles. indicating a homogeneous distribution of the drug over the surface of the vehicle. This represents 57

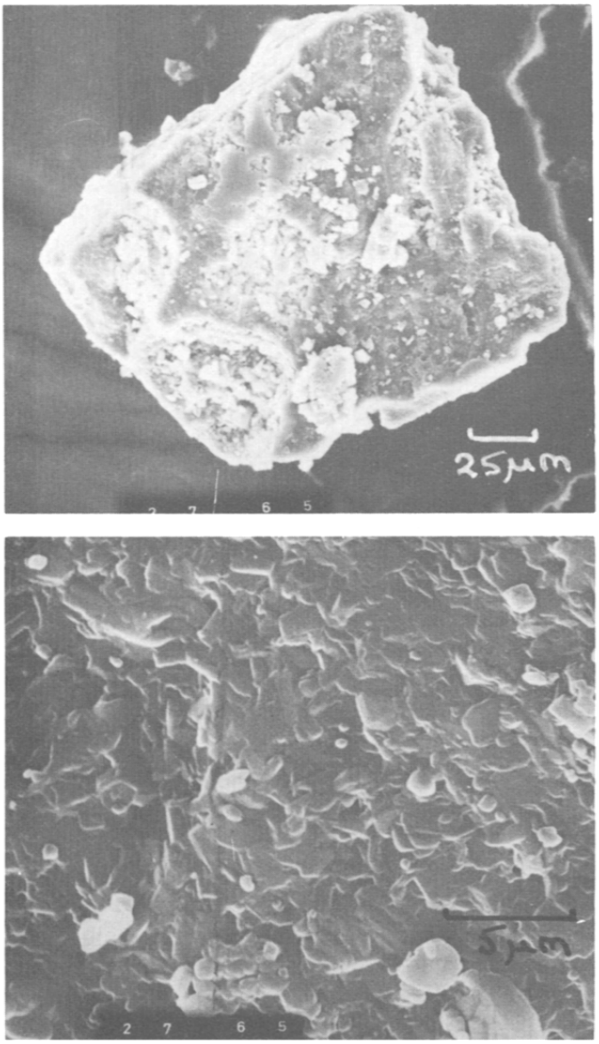

Fig. 7. Scanning electron micrographs of a Dipac particle (180 - 250-μm sieve fraction).

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