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Powder mixing in direct compression formulation by ordered and random processes

M. C. R. JOHNSON*

Upjohn Limited, Crawley, West Sussex RH10 2NJ, U.K.

The mixing processes taking place in a two component system involving a cohesive drug, tetracycline and a direct compression vehicle, spray dried lactose (SDL), have been studied by chemical analysis of powder samples and fluorescence microscopy. At a drug concentration level of 0·25% w/w, both random and ordered mixing is taking place. Mixture quality is better (Cv = 1%) using a fine grade of crystalline lactose (CL) than with SDL (Cv = 4%). Using fractionated material, it was found that SDL between 106 and 300 μm gave Cv values up to 12%, whereas with SDL below 106 μm values of 2% were obtained. The poor quality of the SDL mixtures is attributed to ordered unit segregation.

The production of tablets and capsules of acceptable content uniformity is largely dependent upon the quality of the intial powder mixture. The controlling influence of drug particle size on homogeneity and also the dependence upon sample size are well known (Train 1960). Although less well understood, the type of excipient and its physical characterisitics have been shown to have a profound effect upon mixture quality (Johnson 1973, 1975; Hess et al 1975). The recent introduction of the concept of ordered mixing (Hersey 1975; Yip & Hersey 1977) provides a clearer understanding of the practical situation encountered in pharmaceutical systems in which drug and excipient particles adhere to one another forming mixed agglomerates.

The present study describes investigations into the mixing processes taking place in a two component system involving a cohesive drug and a free-flowing, direct compression vehicle.

MATERIALS AND METHODS

Mixing studies were carried out using tetracycline and a range of excipients including a direct compression grade of spray dried lactose (SDL), crystalline lactose (CL) and starch. For all studies, mixtures containing 0·25% w/w tetracycline were examined and sampled at the scale of scrutiny of 100 mg. Hence, mixtures could represent a low dose formulation for 100 mg tablets containing 250 μg of drug.

To study the influence of particle size on mixture quality, the SDL was divided into two fractions using a Russel Finex shaking sieve of 106 μm. Particle size distribution data for all materials was obtained using an Alpine air jet sieve (Table 1).

* Present address: Siegfried Ltd., CH-4800 Zofingen, Switzerland.

Mixing experiments with tetracycline and SDL were carried out using the following four mixers: Turbula (Type 2C), Patterson Kelly (PK) Blender four quart size and eight quart size, Hobart AE 125 Planetary Mixer. In each case ingredients were prescreened through 300 μm sieve to remove any agglomerates and the mixing vessel was charged so that the drug was placed initially in the centre of the batch. Studies with fractionated SDL, starch and CL were carried out using the Turbula mixer.

Sampling

In order to avoid the problems associated with the use of bulk powder thieves, the powder mix was loaded into a tablet machine hopper. This was set to discharge the batch in 30 min and samples were withdrawn from the powder stream at one minute intervals. By this method samples representative of the whole batch were obtained and are taken under conditions very similar to the conditions of tablet manufacture.

Analysis

By analysing 30 samples at each time point a reasonably precise estimate of mixture composition can be obtained. The confidence limits ($P = 0{\cdot}95$) for a coefficient of variation from 30 samples are 0·8 to 1·34 about the estimate.

The tetracycline content of mixture samples was determined by ultraviolet spectroscopy. Tetracycline in water has an extinction maximum at 275 nm, E(1%, 1 cm) = 337. For the analysis, 100 mg powder samples were dissolved in 25 ml of water and the resulting solutions scanned automatically using a wavelength programmer and Samplomat attachment in conjunction with the spectrophotometer.

Table 1. Particle size data showing cumulative percentage oversize values (Alpine).

Sieve size (μm)	Cumulative % oversize					
	SDL	SDL Under-size	SDL Over-size	CL	Starch	Tetra-cyline
300	0	—	0	—	—	—
212	2·3	—	12·0	0·3	—	—
150	14·2	—	49·0	2·0	—	—
106	31·0	0	88·7	6·3	0·3	—
75	56·7	21·2	100·0	17·2	0·7	—
63	76·3	51·7	—	27·2	1·0	—
53	83·3	67·3	—	33·4	1·7	1·0
45	88·3	74·3	—	39·4	3·3	2·7
20	—	—	—	90·5	65·0	50·0

To investigate the disposition of drug within lactose mixtures, an analysis of drug content of fractionated samples was carried out. Representative samples from a batch were obtained using a spinning riffler. These samples were treated on the Alpine sieve for 6 min and the oversize fraction weighed, dissolved in water and analysed for drug content, as previously. This procedure was repeated for a range of sieves up to 300 μm.

Microscopy

The distribution of drug particles throughout the various mixtures has also been examined using fluorescence microscopy, The fluorescent nature of tetracycline allows very easy differentiation of drug and excipient particles under ultraviolet illumination. The mean exciting wavelength for tetracycline is 390 nm and the mean wavelength of fluorescence is 440 nm. A Leitz Ortholux II microscope was used with an incident light fluorescence facility. To produce optimum photomicrographs a technique of double exposure was developed. It was found that an 8 min exposure time using incident illumination only was required to record the position of tetracycline particles within the frame. Normal transmitted light was then used to illuminate the excipient particles, which could be photographed by re-exposing the frame for a further 2 min.

RESULTS AND DISCUSSION

The results for tetracycline with SDL using the different mixers are given in Fig. 1. Batch sizes vary according to mixer from 1 to 5 kg. Sampling at 5 min intervals indicates that between 20 and 30 min all four mixers have achieved a coefficient of variation (Cv) of between 3 and 4%. With the large PK blender, agglomerates of drug were visible in the mixture at early time points, hence sampling was delayed until 15 min. The result achieved after 20 min is equivalent to the other mixers. Further mixing of the 4 kg batch in the Hobart to 45 min, indicates stability of the mixture as the Cv remains virtually unchanged from the 25 min result. The mixing operation in the Hobart was repeated using a second batch of 4 kg and the results were equivalent within the limits of experimental error, a Cv of 3·4% resulting after 25 min.

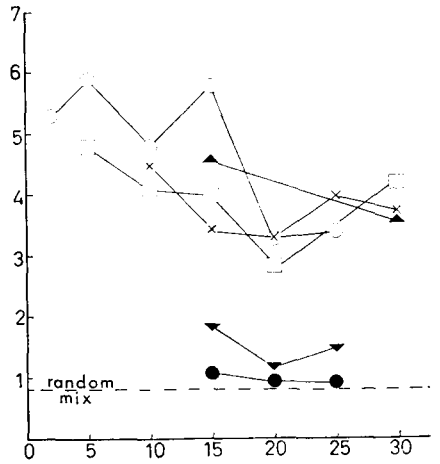

FIG. 1. Cv results for tetracycline mixtures as a function of mixing time. Ordinate: Cv (%). Abscissa: mixing time (min). ○ SDL in Hobart (4 kg); X SDL in PK 4 quart (1·5 kg); ▲ SDL in PK 8 quart (5 kg); □ SDL in Turbula (1 kg); ▼ Starch in Turbula (1 kg); ● CL in Turbula (1 kg).

The theoretical random mix value for these mixtures was estimated from the particle size distribution data for tetracycline (Johnson 1972). The value obtained for 0·25 mg of tetracycline in 100 mg samples was Cv = 0·8%, taking the drug density as 1·44 g cm^{-3} (Beckman pycnometer). Hence, none of the results for SDL mixtures fell within range of the random mix value. It was confirmed by microscopy that the system does not fulfill the criteria for random theory to apply, that is, non-interaction between drug and excipient particles. In fact, association of drug particles with the larger lactose particles is clearly visible from fluorescence microscopy. Thus, some proportion of the drug is being mixed with the lactose by means of ordered mixing. In theory, this should be advantageous with regard to mixture quality and a Cv better than the calculated random mix value should be attainable (Hersey 1975; Coelho & Harnby 1977). In this case where the theoretical value is 0·8%, it would be unlikely that a result better than this would be obtained, since experimental error due to analytical technique would be of this order. However, the experimental mixing

results should at least approach the random mix value.

In an attempt to improve the mixture quality other excipients were investigated, since from previous experience it was known that starch may produce better results than lactose (Johnson 1975; Hess et al 1975). The results using starch and a fine grade of CL (mean particle size 40 μm) are included in Fig. 1. A significant improvement in quality was observed in both cases and Cv values approaching 1% and within range of the theory value were obtained after 15 to 20 min mixing.

The analysis results for fractionated mixtures show that tetracycline remains associated with all size fractions of lactose, even after the 6 min sieving time (Table 2). Expression of the analytical results in terms of drug concentration per fraction, thus taking account of the varying amounts of lactose in each fraction, shows that the larger SDL particles have

Table 2. Tetracycline distribution in SDL and CL from chemical analysis.

Sieve size (μm)	Cumulative % oversize: Tetracycline in SDL mixture	Tetracycline in CL mixture
300	0	—
212	0·24	0
150	9·93	0·18
106	24·85	0·26
75	47·64	0·94
63	55·66	1·58
53	61·71	2·02
45	66·81	3·46
20	87·48	61·06

much more drug associated with them than equivalent sized CL particles. For example, above 45 μm the SDL fractions have up to ten times more drug associated with them (Table 3). Estimates of the amount of tetracycline per unit area of lactose, assuming spherical particles do not indicate a constant value through the range of particle size fractions either for SDL or CL.

From the analytical data for fractionated SDL (Table 2) new theoretical Cv's can be calculated for two extreme cases. Firstly, it can be assumed that all drug present in a particular fraction of SDL is in the form of drug agglomerates of size equal to the average fraction diameter. The calculated Cv from the distribution data so generated is 5·9%. The other extreme case is where the drug associated with a particular lactose fraction is assumed to be evenly

Table 3. Tetracycline concentration (% w/w) within lactose fractions, from chemical analysis.

Fraction range (μm)	Average size (μm)	Tetracycline in SDL mixture (% w/w)	Tetracycline in CL mixture (% w/w)
(300–212)	256	0·130	—
(212–150)	181	0·105	0·025
(150–106)	128	0·139	0·005
(106–75)	90	0·178	0·015
(75–63)	69	0·139	0·014
(63–53)	58	0·513	0·012
(53–45)	49	0·319	0·041
(45–20)	32	0·661	0·271
(<20)	10	1·127	1·185

dispersed over the lactose particles, that is in a truly ordered situation. It is then possible to derive the Cv for a randomly distributed mixture of coated particles from estimations of the average weight of drug per lactose particle in each fraction. The resulting Cv is 0·2%. Comparison of the practical results for SDL mixtures show the values of Cv between 3 and 4 per cent indicate a situation better than the agglomeration but much worse than an evenly coated or ordered situation.

To investigate the influence of excipient particle size on mixture quality, the SDL was divided into undersize material (0–106 μm) and oversize material (106 μm–300 μm) (Table 1). The mixing results for these fractions are given in Fig. 2. Clearly, the removal of material above 106 μm has a beneficial

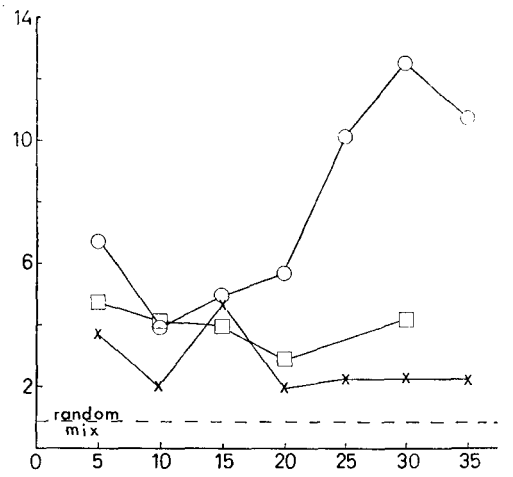

FIG. 2. Cv results for tetracycline mixtures with fractionated SDL as a function of mixing time in Turbula (1 kg). Ordinate: Cv (%). Abscissa: Mixing time (min). ○ Oversize SDL (>106 μm); × Undersize SDL (<106 μm); □ Unfractionated SDL.

effect on SDL mixture quality. The Cv of around 2% from 20 to 35 min mixing time is the best result obtained for any of the SDL series. The oversize fraction exhibits severe deterioration in quality after 15 min with a Cv of 12% after 30 min.

From microscopy, it is apparent that the larger SDL particles from 60 μm upwards have large amounts of drug associated with them. Particularly the spherical particles between 60 and 150 μm appear very brightly fluorescent under uv examination. The distribution of drug in CL samples appears more even in that such brightly illuminated particles are not seen. It is also possible to discern free, unbound drug particles in both lactoses. Agglomerates of drug particles were extremely rare in both systems.

From the available evidence it appears that tetracycline and lactose mixtures involve both ordered and randomly distributed drug particles. In the case of SDL, the uneven distribution of drug with respect to excipient particle size causes a deterioration in mixture quality which must be due to segregation of ordered units within the mixture (Yip & Hersey 1977). This is confirmed by the observation that the oversize SDL produces a very poor quality mixture with very high content variation on longer mixing times. On becoming coated with drug the large lactose particles become significant entities of drug in themselves and variation of these drug units within a sample withdrawn from the mixture can lead to poor uniformity of content.

CONCLUSIONS

The microscopy results confirm that tetracycline is present in the mixtures associated with the surface of lactose particles and also as primary drug particles, freely distributed between the lactose. Thus, mixing is being achieved by both ordered and random processes.

Better quality mixtures are produced using the finer grade CL or starch rather than SDL. The analysis results for fractionated mixtures indicate that the larger size fractions of SDL contain much higher quantities of drug than the equivalent sized CL fractions. The presence of these drug-rich fractions appears to be the cause of the poor mixing results, since the SDL material less than 106 μm gives good results while the material from 106 to 300 μm gives extremely poor results. This is clearly an example of ordered unit segregation (Yip & Hersey 1977). In some recent work with direct compression vehicles (Crooks & Ho 1976) it was suggested that for a satisfactory ordered mixture to be constructed the vehicle should be close to monodisperse. These authors found that "Celutab", a polydisperse dextrose-maltose vehicle, with 2% drug added gave poor results, whereas drug with certain size fractions of "Celutab" gave good quality mixtures. It may be that with CL possessing a narrower distribution of sizes, the drug coating process is more even, therefore aiding the mixing process. The forces responsible for adhesion between drug and excipient particles include Van der Waal's forces, electrostatic and surface forces. The surface characteristics of SDL are very different from CL, particularly the truly spherical spray dried components (Fell 1972). Hence, it would be expected that the surface component of the adhesive forces would differ between the two lactoses. Higher surface adhesive forces may therefore be the explanation for the formation of the drug rich fractions in SDL and the higher unit drug component compared to CL particles.

The results of this study emphasize the significance of particle size and distribution characteristics of direct compression vehicles where low dose mixtures are being formulated. To realize the benefit of the ordered nature of such mixtures it is essential to avoid ordered unit segregation.

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