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THE DESIGN OF A DIRECT COMPRESSION TABLETING EXCIPIENT

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INTRODUCTION

Direct compression tableting has several advantages over tableting processes involving preliminary wet granulation or dry granulation (1). Direct compression is most easily applied to pharmaceutical systems with a high proportion of excipient in the tablet, but in this situation excessive dosage variation (2) is a potential hazard with high potency, low dose drugs. Although segregation of excipients from drugs may also occur with wet granulations (3) (4) the completely free movement of particles in a direct compression random mix means that any segregating tendency during mixing or processing almost inevitably produces dosage variation. However, Hersey(5) has shown that the freedom of movement of drug particles in a direct compression mixture can be reduced by ordered mixing. In an ordered mix, fine particles of drug particles in a direct compression mixture can be reduced by ordered mixing. In an ordered mix, fine particles of drug can adhere to coarser excipient particles and when interparticulate forces are strong enough to keep the drug particles adhered to the excipient particles during processing, segregation of the two systems may be greatly reduced. One factor which influences the formation of stable ordered mixes is the roughness, or porosity of the carrier particles surfaces (6).

The term 'crystal habit' is a description of the outer appearance of a crystal. If the environment of a growing crystal affects its external shape without changing its internal structure, a different habit results. These external changes in appearance are caused by factors which interfere with the uniform approach of crystallising molecules to the different faces of the crystal. A change in the relative growth rates, however small, will ultimately affect the final crystal habit (7). In general, the rate of cooling, degree of supersaturation, mother liquor impurities and the nature of the crystallising solvent all affect the crystalline habit (8). Several habit modifications caused by a change of solvent have been reported (9). Inclusion of a water miscible organic solvent in the crystal mother liquor has been used to produce a crystalline lactose excipient with increased surface irregularities (10).

In an attempt to produce a direct compression excipient which would form non-segregating ordered mixes with drug particles, we have studied the dependence of crystal habit on growth conditions. The excipient produced by this crystallisation technique was compared with another direct compression tableting excipient, anhydrous lactose, in its ability to withstand segregation due to vibration in two model systems.

METHODS AND MATERIALS

Initially, small-scale experiments were carried out to determine the optimum crystal growth time, degree of supersaturation and quantity and type of co-solvent to be added in order to produce crystals of the required particle size and habit. The material investigated was mannitol. Crystallisation was induced by adding either acetone, industrial methylated spirit, propan-1-ol, or propan-2-ol as a co-solvent (all of laboratory grade, Fisons Scientific Apparatus, Loughborough, U.K.).

Following this first set of experiments, larger batches of crystals were prepared by six different methods:

Method 1. A supersaturated solution was prepared containing 200g of mannitol powder in 600ml of water at 50°C. Crystallisation was accomplished by adding 60ml of industrial methylated spirit as a co-solvent. The solution was cooled to 25°C in a water bath and the crystals were grown for one hour, during which time the solution was undisturbed. The resulting crystals were extracted from the mother liquor by filtration. The crystals were dried at 50°C under a vacuum of 400 mm Hg.

Method 2. The supersaturated solution was prepared as in Method 1. However, the crystallisation process involved the addition of 20g of mannitol seed crystals of particle size 75 - 150 μm followed by the immediate addition of 60ml of industrial methylated spirit and subsequent cooling to 25°C. The growth time and methods of extraction and drying were those used in method 1.

Method 3. This method was identical to that described in method 2 except that the solution was agitated very gently for one minute at five minute intervals using a magnetic stirrer. This facilitated growth within the bulk of the solution by dispersing the crystals as they sank to the bottom of the crystalliser.

Method 4. Using the growth conditions of method 3, seed crystals in the particle size range 150 - 210μm were introduced. The increase in seed size from 75 - 150μm was an attempt to alter the handling characteristics of the final crystals by giving them denser centres.

Method 5. Again the growth conditions of method three were used, but the mechanical agitation was replaced by intermittent ultrasonic vibration. The water bath was replaced by an ultrasonic bath operating at a frequency of 25 kHz. During crystal growth the mother liquor was subjected to ultrasonic vibration for one minute at five minute intervals.

Method 6. The crystals were grown as in method 5 except that the ultrasonic vibrations were maintained continuously throughout crystal growth.

All six batches of crystals were stored at 22°C and 50% relative humidity following drying. The six batches were analysed by stereo optical microscopy and stereo electron microscopy to assess the degree of surface irregularity produced by the different techniques. The pore size distribution of mannitol was also measured using mercury intrusion porosimetry (Coulter series 610, Micromeritics Corp., Georgia, U.S.A).

The recrystallised mannitol was compared with anhydrous lactose in its ability to prevent segregation of a model drug, potassium sorbate. A 1.5 kg batch of recrystallised mannitol was prepared according to method 4. This large batch of crystals was passed through a 500 μm sieve.

The two excipients, mannitol and anhydrous lactose, were mixed separately with 1% micronised potassium sorbate in a Y-cone blender (Erweka, Frankfurt, West Germany). The positions of the particles of potassium sorbate on the excipient particles were located by x-ray energy dispersive analysis under the scanning electron microscope (Cambridge 150a, Cambridge Instruments, U.K.).

The resistance of the two mixes to vibrational segregation was assessed using two model systems, one to measure the radial segregation of drug from excipient, and the other to measure the vertical segregation. The radial segregation model consisted of a sieve holder without any sieve mesh. A base unit was stacked beneath the sieve holder and a lid was placed on top of the nest to prevent powder leaving the cylinders during vibration. A specially designed perspex sampling plate was used as a grid, through which 20 samples could be withdrawn. The sampling plate had 50 holes of approximately 1cm diameter drilled in it, so that the holes were equal distances apart and formed a sampling matrix covering the whole sieve holder area. To remove samples, the perspex grid was placed over the sieve holder and located by an overlapping collar. Subsequently, samples were removed from 20 pre-selected positions using a 5ml sample thief. Systematic sampling was carried out both before and

after vibration of each powder mix. Each sample was accurately weighed and the amount of potassium sorbate present was determined by U.V. analysis according to the method of the British Pharmaceutical Codex (1973). The sieve holder and the base unit were vibrated on a sieve shaker (Endecott Ltd., London, U.K) for different time intervals. The amount of radial segregation produced by the vibration was assessed by comparing the statistical coefficients of variation of a second set of twenty samples from the powder bed, according to the method of Johnson (11).

A modified jolting volumeter (J. Engelsmann, Ludwigshafen am Rhine, W. Germany) was used to measure the vertical segregation of the powder mix according to the method of Rees & Staniforth (12). Each powder mix was vibrated 15,000 times in a brass cylinder. Subsequently twenty samples were removed from the whole length of the tube at different depths. The quantity of drug in each sample was again determined by U.V. analysis, and the amount of vertical segregation produced by the vibration was assessed from the coefficient of variation of the twenty samples. Four replicate determinations of the coefficient of variation were carried out using different powder mixes.

Results and discussion

The initial small-scale crystallisation experiments showed that the type of co-solvent used to induce nucleation and subsequent crystal growth had little effect on the crystal habit produced. However, it was found that an excessive amount of co-solvent produced very small, friable crystals of mannitol which on drying appeared as individual dendrites. Conversely, very small quantities of co-solvent did not induce rapid crystal growth and therefore dendrite growth was not enhanced. Observation of the dried crystals using the light microscope indicated an optimum growth time of 60 minutes as this allowed the crystals to grow to a harvestable size. Longer times seemed to have little effect on the size of the crystals or the yield. For the batches of recrystallised mannitol produced

by different crystallisation methods, table 1 shows the percentage yields as a function of the particle size distribution of the excipients.

The crystals produced by method 1 gave poor results, in that the total yield was low and the majority of the crystals produced (88.6%) were single dendrites, less than 300 µm diameter (Table 1). No results were obtained with crystals from method 2 as they did not grow within the bulk of the mother liquor but tended to form a cake at the base of the crystalliser. Method 3 produced an increased total yield, probably caused by the presence of seed crystals increasing the growth pressure by improved nucleation. Of the crystals recovered over 50% passed through a 300 µm sieve. This could be due to several possible effects. (i) The crystals may tend to grow as single dendrites instead of radiating out from the seed crystal. (ii) The action of the mechanical stirrer may adversely affect crystal growth, breaking up crystals into individual dendrites. (iii) The crystals may have been fractured during sieving.

TABLE 1

Particle Size Analysis of Crystals Recovered from Methods 1 to 6 expressed as a percentage of the total yield.

Method	% yield in selected size ranges (µm)			
	300 - 500	500 - 710	710 - 850	>850
1	9.3	1.1	0	0
2	No crystals recovered			
3	15.3	6.3	11.6	9.7
4				
5	10.8	14.0	9.0	8.3
6	11.4	15.6	14.0	0

Observation of the crystals produced in the initial screening experiments indicated that the last two reasons are the most probable explanations and this is supported by the results obtained from crystals made by method 4. The increased yield and greater percentage of larger size fractions in this batch indicated that increasing the size of the seed crystals imparted greater stability to the final crystals, making them less friable.

Ultrasonic vibration causes intense agitation of a liquid at its surface, but without effectively moving or dissipating energy into the bulk of the liquid (13) thus providing a considerable advantage over conventional methods such as the magnetic stirrer, which produce good bulk agitation (which in this case only appears to damage the crystals) but is unable to prevent wall deposition. Ashley, (14) also showed that ultrasonic waves affect the size of the crystals produced. He demonstrated a gradual reduction in size with increasing ultrasonic power which was attributed to an increase in initial nucleation. The total yield of crystals from methods 5 and 6, in which ultrasonic vibrations were used was greatly increased. However, in both cases over 50% of the yield was below 210 μm particle size. This may have been due to the ultrasonic vibration, although further work suggested that this was unlikely. A comparison of crystals produced by methods 5 and 6 in terms of size analysis and yield indicated little difference between intermittent and continuous vibration. This may be because the ultrasonic vibration exerts its main effect by increasing the initial nucleation; subsequent crystal growth appears to be largely unaffected.

A large batch of mannitol excipient was prepared by method 4 because of the overall suitability of the process and the superior individual crystal properties.

The amount of radial segregation produced by vibrating powder mixes containing potassium sorbate and anhydrous lactose or recrystallised mannitol

from batch 4 is shown in Fig. 1. The anhydrous lactose and potassium sorbate mix had a coefficient of variation of 11.02% after only 5 minutes vibration. This increased to 27.78% after 15 minutes. After a vibration time of 30 minutes the powder mix had a coefficient of variation of 37.50%. The particles of anhydrous lactose and potassium sorbate become more segregated as the time of vibration increase. The recrystallised mannitol and potassium sorbate mix produced a small amount of radial segregation when vibrated (Fig. 1). However, this was consistently lower than the segregating tendency of the anhydrous lactose mix, and did not increase with the time of vibration.

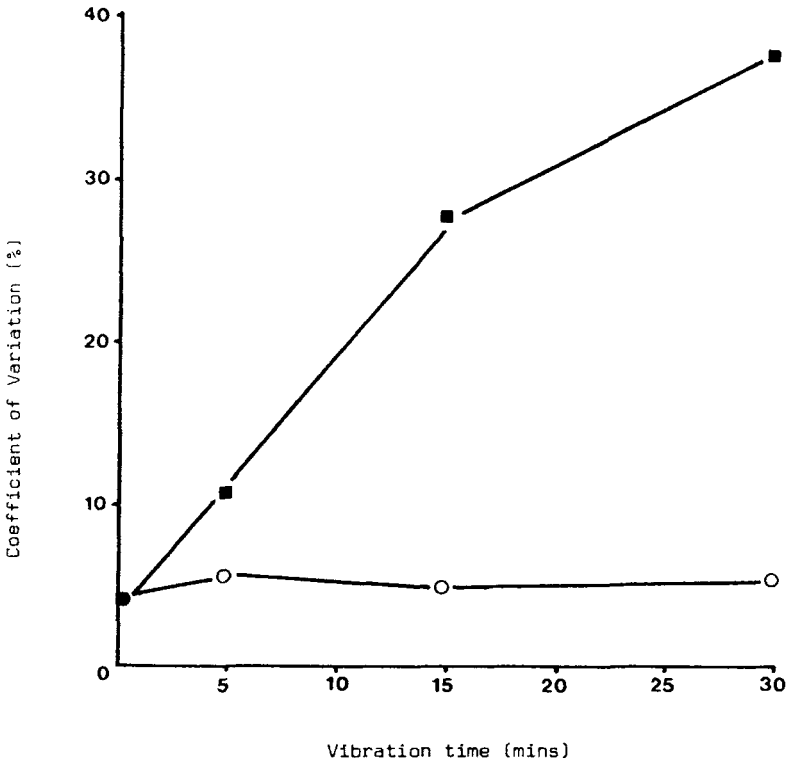

FIGURE ONE

In the vertical segregation model the anhydrous lactose mix again displayed a greater tendency to segregate when vibrated, than the recrystallised mannitol mix (Table 2).

The coefficients of variation following vibration of the two mixes were similar for each excipient in both models. The anhydrous lactose and potassium sorbate had a coefficient of variation ranging from 11.02 to 37.50% in the radial segregation model. The recrystallised mannitol and potassium sorbate powders remained less segregated in both models. In the radial segregation model the coefficients of variation ranged from 4.96 to 5.63% and from 5.44 to 7.30% in the vertical segregation model.

Examination of the surfaces of the two excipients by scanning electron microscopy revealed that the surface of the recrystallised mannitol particles was far more irregular than particles of anhydrous lactose. The highly porous structure of the recrystallised mannitol particles was demonstrated quantitatively using mercury intrusion porosimetry. The pore size distribution of the mannitol excipient is shown in Fig. 2. Over 50%

Table 2

Statistical analysis of the vertical segregation of two powder mixes vibrated 15,000 times in a jolting volumeter

	Recrystallised mannitol		Anhydrous Lactose	
	Before Vibration	After Vibration	Before Vibration	After Vibration
Mean Drug Content (mg)	4.566	4.482	4.615	4.001
True sample variance	0.163	0.286	0.518	0.931
Mean Coefficient of variation	3.567	6.383	11.216	23.270
95% Confidence Limits		± 0.928		± 6.63

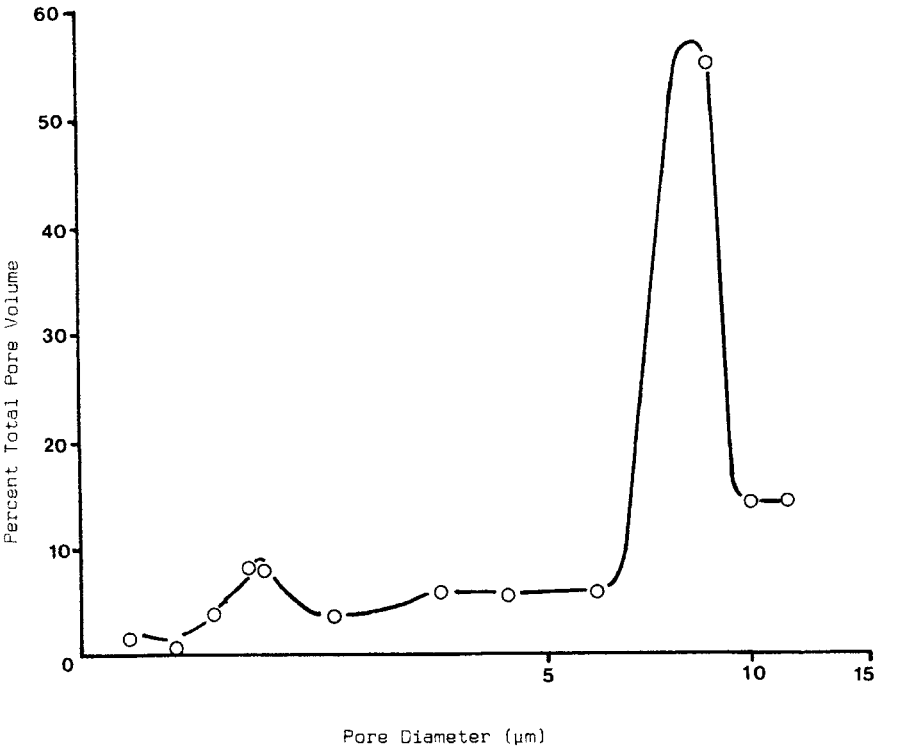

FIGURE TWO

of the mannitol particles had pores with diameters of approximately 9μm. The micronised potassium sorbate particles had diameters of the order of 4 μm. It can be seen that the interparticulate pores on the recrystallised mannitol were large enough to entrap unaggregated potassium sorbate particles.

CONCLUSIONS

In the initial crystallisation tests, the type of co-solvent added to the supersaturated solution to induce nucleation and subsequent crystallisation had little effect on the habit of the crystals produced.

In the preparation of the larger mannitol batches, the addition of

seed crystals immediately after the co-solvent, was found to produce larger crystals of a less friable nature. Although ultrasonic vibration was found to be preferable to mechanical agitation during the growth period, due to increased nucleation, the final size of the crystals was adversely affected. This resulted in a large quantity of very cohesive material being produced, which exhibited poor flow and compaction properties.

The crystallisation conditions which produced mannitol particles with the most useful properties, such as increased porosity, reduced friability and good powder flow properties were those described in method 4. The larger seed crystals, 150-210 μm diameter, used in method 4, produced recrystallised mannitol particles with denser centres which helped to improve the handling characteristics described previously.

A 1% mix of potassium sorbate and recrystallised mannitol was consistently more resistant to vibrational segregation than a mix of anhydrous lactose and the same model drug. In both radial and vertical segregation models, the recrystallised mannitol mix had a maximum mean coefficient of variation of 6.33%, compared with a maximum of 37.50% for a mix of anhydrous lactose and potassium sorbate. The recrystallised mannitol is more resistant to vibrational segregation than anhydrous lactose apparently due to its highly irregular surface which is sufficiently porous to entrap drug particles.

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