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Oxytetracycline tablet formulations: the effect of wet mixing time, particle size and batch variation on granule and tablet properties

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The wet mixing time has been shown to influence the properties of an oxytetracycline dihydrate tablet formulation, wet granulated with PVP solution. Increased time of wet mixing produced larger, stronger and more dense granules, which compressed into tablets with longer disintegration and dissolution times. Decreased drug particle size aggravated these trends. A decrease in drug particle size also produced larger, stronger and more dense granules. Above an oxytetracycline mean particle diameter of about 6 μm, the tablet dissolution was satisfactory. As the oxytetracycline particle size was decreased further, however, the distintegration and dissolution of the corresponding tablets was markedly slower.

In previous papers (Chalmers & Elworthy, 1976, 1976a) the effects of binder volume and concentration, varying the proportion of excipients, and the process of granulation on the properties of granules and tablets of oxytetracycline dihydrate (OTC) have been studied. This paper reports an extension of the work to the effects of wet mixing time, particle size variation, and drug batch variation on the granule and tablet properties.

MATERIALS AND METHODS

250 g samples of the standard bulk supply of OTC (batch B) (Chalmers & Elworthy, 1976a) were ground to a range of mean particle size by (a) use of a pestle and mortar (b) ball milling for 1½ h using porcelain beads (Griffin and George Vibratory Ball Mill) (c) micronized using a Fluid Energy Mill (Gem T Research Model). These samples are designated B_{PM}, B_{BM}, and B_{FE} respectively, They were granulated under the standard conditions, and batch B_{BM} at wet mixing times of 5 and 15 min and compressed into tablets (Chalmers & Elworthy, 1976).

On the basis of microscopic examination of particle size and shape, four other batches of OTC were selected (batches V159, D93, H114, and M118). A sample of

Table 1. *Mean particle sizes of oxytetracycline batches.*

Batch	Mean particle size (μm) from Surface area	Fisher	Microscopy
B	15·0	13·5	13·3
B_{PM}	6·1	7·8	6·2
B_{FE}	2·3	—	—
B_{BM}	1·9	—	—
V159	15·2	18·0	12·6
D93	11·0	13·9	12·9
H114	13·0	15·9	13·4
M118	21·0	16·0	13·5
$M118_{BM}$	2·2	—	—

batch M118 was ball milled to give a sample with a smaller mean particle size (batch $M118_{BM}$). All batches were granulated under the standard conditions using 10 min wet mixing time. Batch M118 was also studied using 5 and 15 min wet mixing time.

Particle size analysis. The mean particle size was obtained by three methods: (a) optical microscopy (British Standard No. 3406 part 4, 1963) giving number average diameter, (b) Fisher Sub-sieve sizer, (c) calculated from the surface area determined by nitrogen adsorption. The mean particle sizes are given in Table 1, and the particle size distributions expressed as log-probability plots in Fig. 1.

RESULTS AND DISCUSSION

There is a reasonable agreement between the mean particle sizes found by the three experimental methods (Table 1). As the results from the surface area measurements are in general lower than those from the Fisher method, it seems likely that fine cracks are absent from the particle surfaces. When unmilled, the particles are rod like, with a length to breadth ratio of approximately 5:1. When milled, symmetrical cube like particles are present. In the discussion that follows, the mean particle size from the surface area method is used, as this method is more sensitive for small particle sizes.

Batch variation of oxytetracycline

In most respects there was no significant difference in the properties of batches made from different batches of the basic drug. Batch H114 did produce slightly larger granules of mean size 300 μm, which compressed into tablets with a disintegration time of 17·2 min and dissolution $T_{50\%}$ time of 6·3 min, both of these being comparatively greater than the mean values given below. Batches B, D93, M118, V159, had a mean and confidence limit at $P = 0{\cdot}95$ respectively of mean granule size 257 ± 29 μm, disintegration time $6{\cdot}4 \pm 2{\cdot}3$ min, dissolution $T_{50\%}$ time $3{\cdot}9 \pm 1{\cdot}9$ min. The granule and tablet properties of these batches (and H114) had the following values: true density $1{\cdot}43 \pm 0{\cdot}03$ g cm^{-3}, apparent density $0{\cdot}91 \pm 0{\cdot}14$ g cm^{-3}, maximum tapped density $0{\cdot}48 \pm 0{\cdot}01$ g cm^{-3}, minimum tapped porosity $66{\cdot}7 \pm 1{\cdot}3\%$, minimum intergranular tapped porosity $47{\cdot}4 \pm 0{\cdot}8\%$, intragranular porosity $36{\cdot}6 \pm 10{\cdot}9\%$, granule strength $4{\cdot}3 \pm 2{\cdot}1$ J $\times 10^{-4}$, tableting pressure 164 ± 5 MN m^{-2}, tablet porosity $10{\cdot}8 \pm 1{\cdot}7\%$, tablet mean pore size $0{\cdot}080 \pm 0{\cdot}017$ μm, breaking load $13{\cdot}5 \pm 1{\cdot}7$ kg.

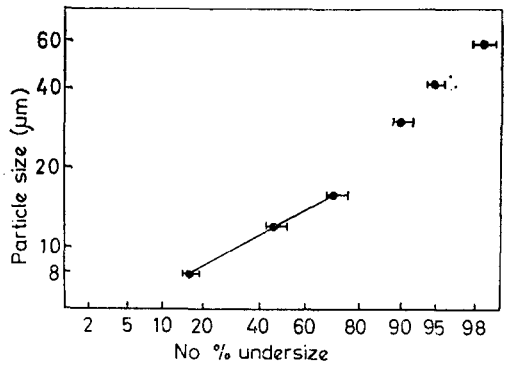

FIG. 1. The particle size distribution of the oxytetracycline dihydrate powder batches. All batches lie within ranges shown.

Table 2. *Effect of varying wet mixing time.*

Batch	M118			B			B_{BM}		
Wet mixing time (min)	5	10	15	5	10	15	5	10	15
(a) *Granule properties*									
True density (g cm^{-3})	1·42	1·42	1·42	1·43	1·43	1·44	1·44	1·44	1·44
Apparent density (g cm^{-3})	0·92	0·95	0·98	0·86	0·90	0·93	0·97	1·06	1·06
Maximum tapped density (g cm^{-3})	0·47	0·48	0·50	0·44	0·46	0·48	0·51	0·53	0·53
Minimum tapped porosity (%)	66·9	66·2	64·8	69·2	67·8	66·6	66·0	63·2	63·2
Minimum intergranular tapped porosity (%)	48·9	49·5	49·0	48·8	48·9	48·6	47·4	50·0	50·0
Intragranular porosity (%)	35·5	32·8	31·1	39·9	37·2	35·2	33·0	26·5	26·1
Mean pore size (μm)	1·34	0·87	0·36	1·21	0·87	0·52	0·20	0·33	0·26
Mean granule size (μm)	215	265	280	180	210	235	410	445	535
Strength ($\times 10^{-4}$J)	2·9	5·4	6·9	3·6	3·9	6·0	5·7	9·8	13·1
(b) *Tablet properties*									
Mean upper punch pressure (MN m^{-2})	163	163	159	160	162	162	159	160	160
Total porosity (%)	10·0	10·8	11·4	10·4	10·6	11·3	13·2	12·5	13·4
Mean pore size (μm)	0·086	0·077	0·072	0·108	0·085	0·042	0·044	0·036	0·037
Disintegration time (min)	1·7	6·0	31·4	1·7	4·4	19·1	4·8	35·8	102·6
Dissolution $T_{50\%}$ (min)	1·4	4·8	19·2	1·6	2·5	8·5	3·4	23·5	39·0
Breaking load (kg)	9·6	13·1	13·2	8·2	10·7	11·6	13·2	14·6	14·4

Batches D93 and H114 gave small granule mean pore sizes of 0·37 and 0·41 μm respectively compared with a mean value of 0·93 ± 0·28 μm for the other batches. However, tableting eliminated these differences as the mean pore size of all tablets was fairly close together.

It appears that variation in the mean particle size of unmilled materials from 11 to 21 μm does not have a dramatic effect on the measured properties. Batches H114 and M118 had an increased proportion of larger particles, while batch V159 contained a significant amount of more symmetrical particles, from microscopic observations. These factors do not appear to be having important effects on the dissolution times of the tablets for the unmilled materials.

Effect of varying wet mixing time

Results on batches B and M118 (mean particle diameters 15 and 21 μm respectively) are given in Table 2. As the time of mixing was increased the granules became larger,

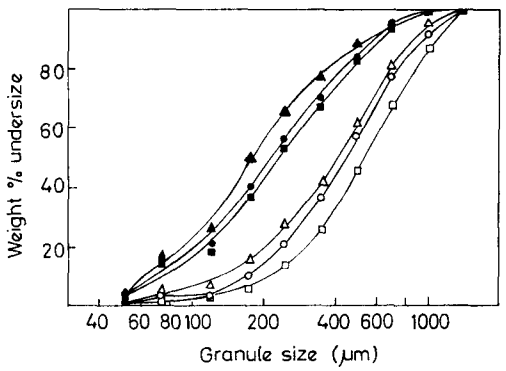

FIG. 2. The effect of wet mixing time on the granule size distribution of batches prepared from both milled and unmilled oxytetracycline dihydrate. Batch B (unmilled): wet mixing time (min) ▲ = 5, ● = 10, ■ = 15. Batch B_{BM} (milled): wet mixing time (min) △ = 5, ○ = 10, □ = 15.

stronger, and more dense. The effect on the granule size distributions is shown in Fig. 2. The mean pore size is much decreased. This is consistent with the findings of other workers, e.g. Ganderton & Hunter (1971), that as the mixing time increases the consolidation of the granules progresses.

Although the porosity of the granules was decreased, the total void space in the tablets made from them did not vary with increased wet mixing time.

Batch B_{BM} (mean particle diameter 1·9 μm) was subjected to the same treatment as the unmilled batches, with generally similar results (Table 2). However, the mean granule sizes were much larger than those of the unmilled batches, and there was more variation between the results obtained after 5 and 10 min wet mixing time compared with 10 and 15 min. The exception is the mean pore size of the granules, which was not as much affected by wet mixing time as that of the unmilled materials. This may be because the asymmetric shape of the unmilled materials helps to resist consolidation, which the more symmetrical particles of the milled material do not. The increase in wet mixing time from 5 to 15 min increased the disintegration time by a factor of 21 and the dissolution $T_{50\%}$ time by a factor of 11. This cannot be explained on the basis of the tablet porosity, which remains unaffected by wet mixing time, within experimental error, nor on the basis of the decrease in mean pore size from 0·044 to 0·037 μm. This result is examined further in the next section, but it is clear that small variations in wet mixing time can grossly affect the performance of a formulation, especially when fine powders are used.

We have previously argued (Chalmers & Elworthy, 1976a) that the dried film of PVP in the tablet structure retards disintegration and dissolution. The longer the wet mixing time, the better would be the expected distribution of PVP in the powder bed. This could contribute to the increased disintegration and dissolution times with increased wet mixing time. It follows for this system that a poor distribution of binder could be advantageous.

Effect of particle size

A 10 min wet mixing time gave the results in Table 3. As the particle size of the oxytetracycline decreased the granules formed from it in a standard mix were larger and stronger. The pore structure was finer. The tablets exhibited a slight increase in strength as the initial drug particle size decreased, but the disintegration and dissolution results were most interesting. It would appear that below a certain mean particle size the dissolution characteristics of the formulation are adversely affected.

Table 3. *Effect of variation in particle size.*

Batch	Mean part. size (μm)	Mean gran. size (μm)	Intra-gran. poros. (%)	Mean gran. pore size (μm)	Granule strength ($\times 10^{-4}$J)	Tablet poros. (%)	Mean tablet pore size (μm)	Disint. time (min)	Dissol. T_{50}% time (min)	Breaking load (kg)
B_{BM}	1·9	445	26·5	0·33	9·8	12·5	0·036	35·8	23·5	14·6
$M118_{BM}$	2·2	355	26·4	0·34	7·7	11·2	0·053	42·9	27·2	14·2
B_{FE}	2·3	290	33·9	0·23	6·1	11·3	0·046	13·6	7·8	16·3
B_{PM}	6·1	255	35·9	0·55	6·1	11·1	0·077	6·3	4·6	12·9
B	15·0	263	34·8	0·91	4·2	10·2	0·087	6·8	4·0	13·4
M118	21·0	265	32·8	0·87	5·4	10·8	0·077	6·0	4·8	13·1

Results which did not vary significantly had the following mean values and confidence limits at $P = 0{\cdot}95$:

Granule properties true density 1·43 ± 0·02 g cm^{-3}, apparent density 0·97 ± 0·15 g cm^{-3}, maximum tapped density 0·50 ± 0·07 g cm^{-3}, minimum tapped porosity 64·9 ± 4·8%, minimum intergranular tapped porosity 47·9 ± 6·3%.

Tablet properties mean upper punch pressure 164 ± 6 MN m^{-2}.

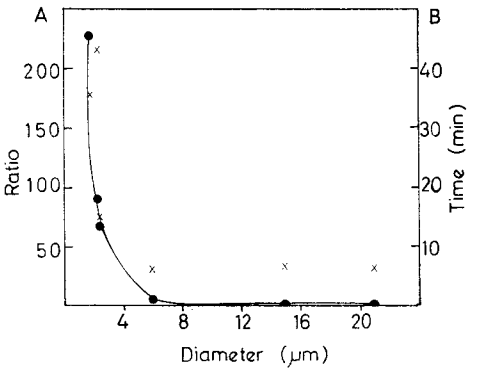

FIG. 3. The correlation of the ratio of number of oxytetracycline particles/number of disintegrant particles (A) with disintegration time (B) for a range of oxytetracycline particle diameters (μm). ● = ratio of number of oxytetracycline to total number of microcrystalline cellulose and alginic acid particles. × = disintegration time.

Using the true densities and particle sizes the number of OTC, microcrystalline cellulose, and alginic acid particles in each dry mix can be calculated. Over the range of OTC particle size studied the ratio: (number of OTC particles)/(total number of disintegrant particles) was evaluated. The ratio is plotted in Fig. 3 against OTC mean particle diameter, and the disintegration time is shown in the same Figure. Bearing in mind that OTC (without disintegrants) when granulated with 30% w/v PVP gave very poorly disintegrating tablets, we can see the reason for the rise on disintegration time at small particle sizes. As a crude approximation we consider a model of the powder bed, assumed to be perfectly mixed. At a mean OTC particle diameter of 15 μm, there are four disintegrant particles for every OTC particle. When the particle size has been reduced to 6 μm there are now five OTC particles for every disintegrant particle. This is apparently sufficient for a reasonable disintegration time. However at around 3 μm the ratio curve starts to turn upwards sharply, and when the OTC mean particle diameter has been reduced to 1·6 μm, there are *ca* 230 OTC particles for every disintegrant particle. The solvent front entering the tablet has to pass through poorly disintegrating OTC before it encounters a disintegrant particle, while at larger OTC particle sizes disintegrant particles are more easily encountered. In addition, at small OTC particle sizes, the solvent has to traverse a tortuous pore structure between the fine OTC particles. Decreasing the particle size to potentially increase bioavailability is only a useful step, if the disintegration and dissolution rates of the tablet are not adversely affected by so doing.

REFERENCES

CHALMERS, A. A. & ELWORTHY, P. H. (1976). *J. Pharm. Pharmac.*, **28**, 228–233.
CHALMERS, A. A. & ELWORTHY, P. H. (1976a). *Ibid.*, **28**, 234–238.
GANDERTON, D. & HUNTER, B. M. (1971). *Ibid.*, **32**, *Suppl.*, 1S–10S.