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Oxytetracyline tablet formulations: effect of variations in binder concentration and volume on granule and tablet properties

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Formulation studies have been conducted on an oxytetracycline dihydrate tablet formulation containing microcrystalline cellulose and alginic acid, wet granulated with polyvinylpyrrolidone (PVP) solution. A range of granule properties including size, strength, packing and porosity, and tablet properties including breaking load, porosity, disintegration and dissolution have been measured. Increased compaction pressure decreased tablet porosity. The reproducibility of the above properties was determined by tests on nine standard batches of granules and tablets. An increased concentration of PVP in the binder solution decreased the rate of tablet dissolution. Although the volume of granulating solution apparently controlled the granule size, it did not significantly alter the tablet dissolution, when the amount of PVP was constant.

The commercial production of oxytetracycline tablets B.P. was known to be susceptible to both inter- and intra-batch variation, particularly in disintegration and dissolution rates. Recent reports (Groves, 1973; Jones, Risdall & Frier, 1974) have suggested that drug availability in this official preparation is variable, especially when different manufacturers' products are compared. The effect of moisture content and gelatin binding agent on certain bulk powder properties on an oxytetracycline formulation have been reported (Esezobo & Pilpel, 1974).

We have initiated a broadly based investigation of the influence of formulation and process variables on both granule and tablet properties. As the potential number of variables was very large it was necessary to be selective. The effect of variations in the volume and concentration of one binder solution, the proportion of certain excipients, the particle size of oxytetracycline, the method of granulation and the wet mixing time were studied.

MATERIALS AND METHODS

The standard formulation was: oxytetracycline dihydrate E.P. 90·1% w/w, microcrystalline cellulose B.P.C. 7·2% w/w, alginic acid B.P.C. 2·7% w/w.

The oxytetracycline dihydrate (ICI Pharmaceuticals Division Ltd.) was of E.P. quality and had a potency of 878 units mg^{-1}. It had a loss on drying at 60° of 3·0% w/w, and a surface area of 0·28 m^2g^{-1}.

A variety of oxytetracycline batches were used and characterized by surface area determinations, by use of a Fisher Sub-sieve Sizer (KEK Ltd.), and both optical and electron scanning microscopy. The microcrystalline cellulose was 'Avicell' PH101 brand (Honeywill & Stein Ltd.). The binder, polyvinylpyrrolidone ['Plasdone' K 29–32, GAF (U.K.) Ltd. (PVP)], was normally added as a 2·5% w/v aqueous solution up to the optimum of 30% v/w. 1% w/w magnesium stearate was added to the dried granules as a lubricant before dry screening. Batch quantities were limited to 166·5 g on average to minimize cost.

Granulation procedure

The powders were added in a fixed order to a sigma-blade laboratory mixer (Model 1Z, Winkworth Machinery Ltd.) and dry mixed for 3 min, a time found to give a satisfactory distribution. The wet mix began with the addition by pipette of half the total volume of binder solution with a similar addition 1 min later. The total wet mixing time was 10 min (see Chalmers & Elworthy, 1976a). The mass was discharged through an oscillating granulator (Model 6, Jackson & Crockatt Ltd.) fitted with a 16 mesh screen. The granules were tray dried for 1½ h at 60°, and the lubricant incorporated by tumble mixing in a jar for 1 min before dry granulation using a 12 mesh screen.

Characterization of granules

Particle size analysis. The particle size distribution of the granules was measured by sieve analysis (B.S. 410 test sieves) and the mean granule size was estimated from the weight % under size *vs* size curves.

True density. The true granule density was measured using an air comparison pycnometer (Model 930, Beckman Instruments Ltd.).

Tapped density. The tapped density of a fraction of granules retained by a 30 mesh sieve but passing a 22 mesh sieve was measured according to Neumann (1967). The measuring tube, approximating in diameter to the tablet die (10·5 mm) was charged with 2·5 g of granules and dropped 200 times through a height of 1 cm.

Apparent density. The apparent density and hence intragranular porosity of $-22 + 30$ mesh granules was measured by a modification of the pycnometric method of Strickland, Busse & Higuchi (1956).

Pore size distribution. The distribution of pores within the same $-22 + 30$ fraction was plotted using a high pressure mercury intrusion porosimeter (Model 820, Carlo Erba Ltd.). Pressure is increased gradually from atmospheric up to 900 atmospheres ($\simeq$ 90 MN m^{-2}). A mean pore size was calculated using the Washburn equation (1921) as described by Rowe, Elworthy & Ganderton (1973).

Granule strength. The force required to fracture $-14 + 16$ mesh granules was measured by the method of Ganderton & Hunter (1971).

Tableting procedure

The granules were compressed at 165 MN m^{-2} using 10·5 mm flat punches on a motorized single punch tablet machine (type F3, Manesty Machines Ltd.) which had been instrumented to permit measurement of the applied pressure. An adaptation of the technique of Shotton & Ganderton (1960) was employed. The results of varying

Table 1. *The effect of compaction pressure on tablet properties.*

Upper punch pressure (MN m^{-2})	Total porosity (%)	Mean pore radius (μm)	Disintegration time (min)	Dissolution time ($T_{50\%}$) (min)	Breaking load kg
23	33·5	0·69	1·1	1·2	1·0
45	27·1	0·45	1·4	1·3	2·6
88	18·4	0·20	1·9	1·9	5·5
165	10·5	0·087	6·2	3·0	13·7
309	5·0	0·023	33·0	43·5	23·2

the compaction pressure on the tablet properties are given in Table 1. A pressure of about 165 MN m^{-2} was chosen as one which gave hard tablets without overcompression.

Characterization of tablets

Breaking load. The compressive load required to cause tensile fracture of the tablets under diametral compression was measured using an Instron instrument (Fell & Newton, 1970) and the mean of five determinations calculated.

Porosity. The total void space was derived from the dimensions and weights of the five tablets used for pore size analysis and the true density of the granules.

Pore size distribution. An analogous method to that for granules was used, the sample comprising five tablets.

Disintegration. Five tablets were individually assessed using the B.P. distintegration test apparatus (Manesty Ltd.) and a mean time calculated.

Dissolution. The dissolution rate of single tablets was measured in 0·1 N HCl at 37° ± 0·5° using apparatus based on the beaker method of Levy & Hayes (1960). Samples were periodically assayed spectrophotometrically at 353 nm for drug in solution. The results of five experiments were averaged.

RESULTS AND DISCUSSION

Each experimental section contained one or more standard batches. These were made from the formulation given, granulated with 30% v/w of a 2·5% w/v PVP solution by the method described. This procedure was adopted to give a reference batch, and to produce statistical information on the variability of the quantities measured. Over 20 months, ten standard batches of granules were prepared, and nine of these were tableted. The mean values and limits of error ($P = 0{\cdot}95$) are as follows:

Granules: True density 1·43 ± 0·03 g cm^{-3}, apparent density 0·89 ± 0·06 g cm^{-3}, maximum tapped density 0·46 ± 0·03 g cm^{-3}, minimum tapped porosity 67·6 ± 2·6%, minimum intergranular tapped porosity 48·1 ± 3·2%, intragranular porosity 37·5 ± 0·7%, mean pore size 0·82 ± 0·23 μm, mean granule size 248 ± 46 μm, granule strength 4·0 ± 2·1 × 10^{-4}J.

Tablets: Upper punch pressure 163 ± 6 MN m^{-2}, total porosity 9·5 ± 1·5%, mean pore size 0·081 ± 0·016 μm, breaking load 13·1 ± 3·2 kg.

None of the above properties varied significantly with time. Table 2 indicates that there is a change in disintegration times and dissolution rates with time. Batches made

Table 2. *Disintegration and dissolution times for standard batches of tablets.*

Batch code	Date of manufacture	Disintegration time (min)	Dissolution time, $T_{50\%}$ (min)
C2	Oct. 73	10·3	5·5
C5	Oct. 73	13·5	5·8
F2	Mar. 74	7·8	4·2
F3	Mar. 74	7·6	4·2
G5	Apr. 74	6·6	2·9
H2	June 74	3·7	2·3
J2	June 74	3·5	2·3
K2	Nov. 74	4·4	2·4
M6	Jan. 75	5·8	3·6

only a few days apart (C2, C5 and F1, F2) show a reasonable agreement, but over the 20 month period there is a decrease in these quantities until the results appear to be random. The limits of error were calculated for the last five batches only, giving disintegration time 4·6 ± 3·0 min, dissolution $T_{50\%}$ 2·7 ± 1·6 min. To apply these limits to earlier batches where the disintegration times and dissolution rates differed significantly, it was assumed that the same percentage variation about the mean occurred.

In an investigation into the causes of this variation it was found that the moisture content did not vary significantly with the date of manufacture in the batches of granules and tablets. No significant chemical decomposition is reported for oxytetracycline dihydrate stored in the dark in closed containers at 20°. Substitution of an additional unbiased experimental operator did not alter the results. The same materials were used throughout, and the granulation and tableting operations were as tightly controlled as possible. While subtle changes in the surface properties of the oxytetracycline particles with time might be responsible for this behaviour, it seems more likely that changes in the wet mixing time are responsible.

The properties of this particular granulation are very sensitive to the length of the wet mixing time (Chalmers & Elworthy, 1976b); for this batch of drug a variation of 0·1 min in the wet mixing time gives approximately 1½ min change in disintegration time and over ½ min change in dissolution $T_{50\%}$ time. As the mixer used was a new one, there may be frictional changes occurring during a "running in" period, resulting in slight changes of energy expended in the wet mix stage. This could be an important point in controlling industrial granulations which are sensitive to the wet mixing time.

To assess the effects of the binder solution on the properties of the granules and tablets, three sets of experiments were carried out: (a) Increasing the PVP concentration using a constant volume of granulating solution, (b) Increasing the volume of granulating solution at a fixed PVP concentration, and (c) Increasing the volume of

Table 3. *Effect of varying the concentration and volume of granulating solution on the granule and tablet properties.*

	Granulating solution		Mean granule size (μm)	Disintegration time (min)	Dissolution time $T_{50\%}$ (min)	Breaking load (kg)
	% w/v PVP	Volume used % v/w				
(a)	0	30	360	1·3	1·7	10·5
	1·25	30	210	3·6	2·3	14·3
	2·5	30	240	10·3	5·5	14·9
	5·0	30	250	12·3	17·5	13·7
(b)	2·5	21	125	2·5	1·7	11·9
	2·5	30	235	6·7	5·5	14·0
	2·5	39	720	24·4	13·7	13·6
(c)	3·57	21	160	4·3	2·7	14·4
	2·5	30	270	13·5	5·8	15·1
	1·92	39	565	9·1	6·1	17·9
	1·67	45	950	5·3	4·7	14·3

The remaining granule and tablet properties showed no significant variation in the three experimental sequences listed above. Quoting the mean results in the order given in the table gives for the granules: true density (g cm^{-3}): 1·44, 1·45, 1·45, apparent density (g cm^{-3}), 0·88, 0·87, 0·88, maximum tapped density (g cm^{-3}) 0·46, 0·46, 0·46, minimum tapped porosity (%) 68·4, 68·2, 68·4, minimum intergranular tapped porosity (%) 49·1, 48·4, 48·8, intragranular porosity (%) 39·1, 40·0, 38·8, mean pore size (μm) 0·82, 0·94, 0·79. and strength (× 10^{-4}J) 2·6, 4·7, 3·8.

For the tablets: compaction pressure (MN m^{-2}) 162, 165, 165, total porosity (%) 9·9, 8·8, 9·0, mean pore size (μm) 0·084, 0·067, 0·070.

granulating solution while decreasing the PVP concentration to give the same amount of PVP in each granulation.

For set (a) the most important effects are the increase in dissolution and disintegration times (Table 3). As the mean pore size and porosity of the tablets did not vary with PVP concentration, it appears that the increase in dissolution and disintegration times are due to a heavier coating of the powder particles with PVP at the higher concentrations. This may act by slowing the rate at which invading water reaches the surface of the powder particles, and slowing diffusion away from the surface of the oxytetracycline, due to the higher viscosity of PVP solutions compared with that of pure water. The ability of the excipients to promote disintegration could also be delayed. Tablets prepared by granulation with pure water are significantly weaker than those prepared with PVP in the granulating liquid. The granule size distribution is shown in Fig. 1. Changing the granulating liquid from water to 1·25% w/v PVP solution caused a decrease in the mean granule size. As the surface tension of this solution is 63 compared with 72 mN m^{-1} for water, the powder mixture may be better wetted than by pure water, giving increased solid/liquid adhesion compared with solid/solid adhesion, with a decrease in granule size. Although the surface tension of PVP solutions decreases further as concentration increases, their viscosity rises also. This may affect any further wetting effects and cause the slight increase in the mean granule size shown in Table 3.

In both sets of experiments (b) and (c) the volume of the granulating liquid is increased. No difficulties in distributing the binder solution on the powder was experienced, even for the smallest volume used. Figs 2 and 3 show the pronounced effect on the granule size distribution. The increased granule sizes are in accordance with the results of Ganderton & Hunter (1971). Presumably increasing the amount of liquid increases capillary cohesion in the mass. The effects of increasing the volume of granulating liquid appear to greatly outweigh those of surface tension and viscosity. In sets (b) and (c) there is no significant alteration in the porosity or mean pore size of the tablets. In a similar manner to that observed in set (a) the increased PVP concentration appears to be responsible for the increasing disintegration and dissolution times in set (b).

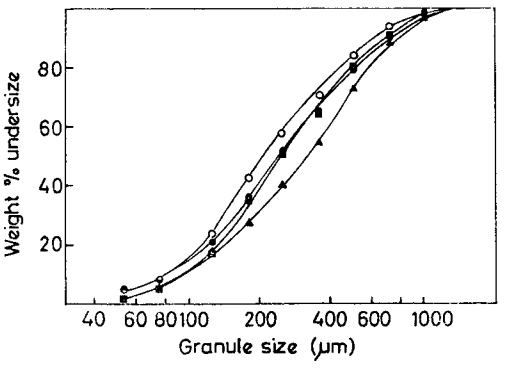

Fig. 1

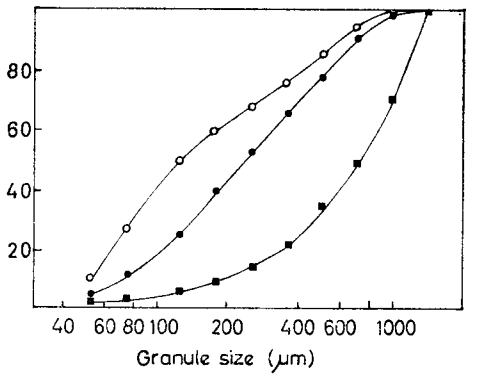

Fig. 2

FIG. 1. The effect of varying the concentration of the binder solution on the granule size distribution. Concentration of PVP solution added: ▲0% w/v, ○ 1·25% w/v, ● 2·5% w/v, ■ 5% w/v (added to 30% v/w in each case).

FIG. 2. The effect of varying the volume of binder solution added on the granule size distribution. Volume of 2·5% w/v PVP solution added: ○ 21% v/w, ● 30% v/w, ■ 39% v/w.

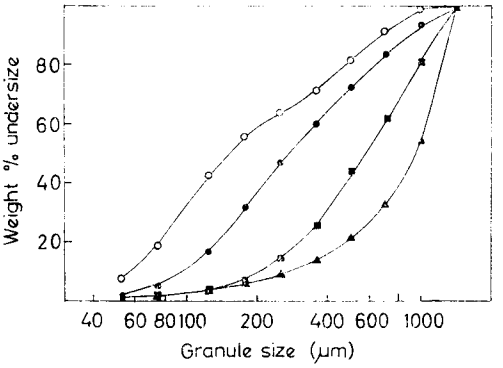

FIG. 3. The effect of varying the volume of binder solution added, with the PVP content constant, on the granule size distribution. Volume and concentration of PVP solution added: ○ 21% v/w, 3·57% w/v; ● 30% v/w, 2·5% w/v; ■ 39% v/w, 1·92% w/v; ▲45% v/w, 1·67% w/v.

The total PVP concentration is constant in set (c) and the values of disintegration and dissolution times do not show the smooth trends observed with the two previous sets of experiments. It can be seen from Fig. 3 that there is much fine material in the 3·57% w/v PVP granulation, and the thickness of the PVP film around each particle before compression may be thinner in this instance, perhaps leading to the more rapid disintegration and dissolution rates observed.

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