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Oxytetracycline tablet formulations: the influence of excipients and the method of granulation

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The proportion of microcrystalline cellulose and alginic acid present as excipients in the dry mix for an oxytetracycline dihydrate tablet formulation, prepared by a conventional wet granulation process, has been shown to influence granule formation and properties. Granule size distributions have varied widely due perhaps to variation in binder distribution. Granulating with water was equally satisfactory to granulating with a PVP solution. Slugged granules produced robust tablets, which disintegrated and dissolved rapidly.

Chalmers & Elworthy (1976) assessed the variability of the properties of granules and tablets of oxytetracycline dihydrate (OTC), and also the effect of varying the amount and concentration of granulating solution. In this paper we examine the effect of varying the proportions of excipients, the effect of water as a granulating liquid, and the effect of omitting wet granulation on the properties of the granules and tablets.

MATERIALS AND METHODS

Unless otherwise stated the materials and methods employed were identical to those described in Chalmers & Elworthy (1976).

(a) *The influence of microcrystalline cellulose and alginic acid.* Half and all the normal amount of each of these ingredients was omitted in turn. To maintain the same volume of liquid to weight of solids ratio, the dry mix was made up to 100% with further oxytetracycline in this and the following sections. Standard binder additions of 30% v/w of a 2·5% w/v PVP solution were used throughout this section.

(b) *Formulations granulated with water.* These were prepared similarly to formulations in section (a) but using 30% v/w water as the granulating liquid.

(c) *Formulations prepared by slugging.* The basic powders were mixed in the Z-blade mixer for 3 min, then 2·5 g samples were compressed at 165 MN m^{-2} (the pressure used for tableting) on a hydraulic press (Type A-14 Apex Construction Ltd.) in a 1·91 cm diameter punch and die set. The briquettes so formed were broken up gradually in a pestle and mortar before passing through a 12 mesh screen. The latter was used in the dry screening of the wet granulations. 1% w/w magnesium stearate was incorporated as lubricant in the usual manner.

RESULTS AND DISCUSSION

(a) *The influence of microcrystalline cellulose and alginic acid*

Figs 1 and 2 show the large extent to which either of these ingredients in the mix influenced the granule size distribution. As the percentage of oxytetracycline was increased, the mean granule size increased (Table 1). No other granule properties altered significantly with variation of microcrystalline cellulose and alginic acid content.

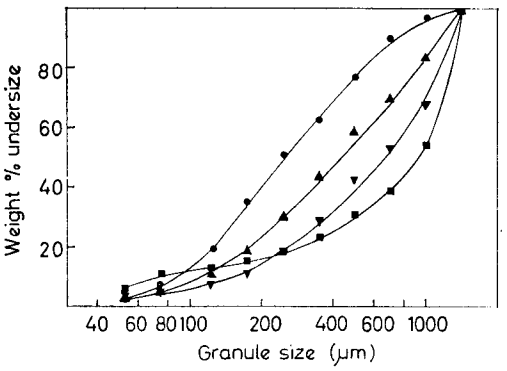

Fig. 1

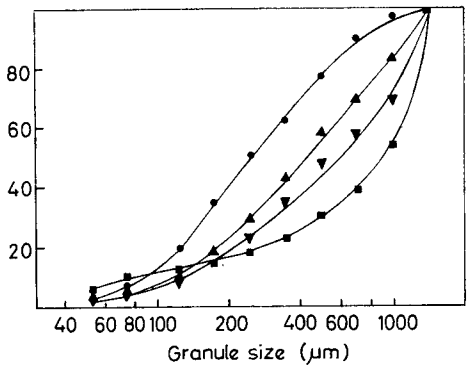

Fig. 2

FIG. 1. The influence of microcrystalline cellulose content on granule size distribution. Amount of microcrystalline cellulose present in dry mix: ■ 0% w/w, ▼ 3·6% w/w, ▲ 7·2% w/w, ● 7·2% w/w with 2·7% w/w alginic acid.

FIG. 2. The influence of alginic acid content on granule size distribution. Amount of alginic acid present in dry mix: ■ 0% w/w, ▼ 1·35% w/w, ▲ 2·7% w/w, ● 2·7% w/w with 7·2% microcrystalline cellulose.

The granulation consisting of oxytetracycline only, which had the greatest mean granule size, compressed to give tablets of low porosity and strength. (Table 1). These factors would be consistent with weaker interparticulate bonding within the granules. The high disintegration time was to be expected from a low porosity tablet without any disintegrating agent. The properties of the tablets were uneven, in that a considerable portion of them would dissolve in a fairly short time, but sufficient aggregated residue persisted, giving large values for the disintegration time.

While both excipients separately decrease dissolution and disintegration times, the presence of both together does not give a further decrease. This may imply that the rate limiting step in the dissolution is the attack by water on the PVP coated surface of the oxytetracycline, rather than the penetration of water into pores or the subsequent disintegration.

The greatest differences in the tablet properties occurred for the addition of either excipient to the pure oxytetracycline. It appears that small variations of excipient content around the concentrations used in the standard formulation will not cause

Table 1. *The effect of varying the microcrystalline cellulose and alginic acid content.*

Ingredients			Mean granule size (μm)	Tablet porosity (%)	Disintegration time (min)	Dissolution time $T_{50\%}$ (min)	Breaking load (kg)
OTC	MC* (% w/w)	AA*					
100	0	0	900	6·6	>60	7·2	8·6
96·4	3·6	0	480	7·8	6·8	2·6	11·9
92·8	7·2	0	340	8·0	5·0	2·3	11·1
98·65	0	1·35	780	6·8	20·7	2·5	9·7
97·3	0	2·7	415	8·6	4·7	2·3	10·0
90·1	7·2	2·7	250	9·1	5·7	2·9	12·7

MC = microcrystalline cellulose, AA = alginic acid.

Properties which did not give variations outside experimental error had mean value for granules: true density 1·40 g cm^{-3}, apparent density 0·86 g cm^{-3}, maximum tapped density 0·45 g cm^{-3}, minimum tapped porosity 67·9%, minimum intergranular tapped porosity 47·9%, intragranular porosity 38·5%, mean pore size 0·96 μm and strength 3·7 × 10^{-4}J.

For the tablets: mean upper punch pressure 164 MN m^{-2}, and mean pore size 0·094 μm.

Table 2. *Properties of granules made by granulating with water and by slugging.*

	Formulation ingredients % w/w			Method of granulation	True density (g cm^{-3})	Apparent density (g cm^{-3})	Maximum tapped density (g cm^{-3})	Minimum tapped porosity %	Minimum intergran. tapped porosity %	Intra-granular porosity %	Mean pore size (μm)	Mean granule size (μm)	Breaking load ($\times 10^{-4}$J)
	OTC	MC	AA										
I	100	0	0	30% v/w Aqueous	1·41	0·86	0·057	59·6	33·7	38·9	0·97	(92)	0·7
II	97·3	0	2·7	"	1·40	0·87	0·44	68·6	49·4	37·6	1·10	420	3·8
III	92·8	7·2	0	"	1·41	0·86	0·42	70·2	50·0	38·0	0·98	290	2·9
IV	90·1	7·2	2·7	"	1·42	0·89	0·47	66·9	47·2	37·4	0·89	250	3·2
V	90·1	7·2	2·7	2·5%w/v 30%v/w PVP	1·40	0·90	0·45	67·9	50·0	36·3	0·78	235	4·7
VI	100	0	0	slugging and breakdown	1·42	1·17	0·75	47·2	35·9	17·8	0·10	440	11·3
VII	97·3	0	2·7	"	1·41	1·15	0·74	47·5	35·6	18·4	0·12	355	10·6
VIII	92·8	7·2	0	"	1·41	1·16	0·74	47·5	36·2	17·8	0·12	305	9·2
IX	90·1	7·2	2·7	"	1·44	1·17	0·74	48·6	36·8	18·6	0·13	310	9·4

Table 3. *Properties of tablets made from granules listed in Table 2.*

Formulation No. (Table 2)	Upper punch pressure (MN m^{-2})	Total porosity (%)	Mean pore size (μm)	Disint. time (min)	Dissol. $T_{50\%}$ time (min)	Breaking load (kg)
I	160	6·5	0·041	>120	~60	8·4
II	165	7·9	0·090	3·8	2·0	9·3
III	168	8·4	0·077	14·7	12·8	10·2
IV	162	9·2	0·087	2·8	2·3	12·0
V	168	9·1	0·072	3·5	2·3	12·3
VI	162	6·9	0·057	>60	~40	7·7
VII	159	7·2	0·077	0·3	1·0	8·9
VIII	162	7·3	0·070	1·9	1·7	7·4
IX	162	6·9	0·064	0·4	0·9	8·0

MC = microcrystalline cellulose, AA = alginic acid.

undue variations in granule and tablet properties. However the granule size is reduced when both excipients are present together; inclusion of alginic acid when the microcrystalline cellulose is present gives a decrease in mean granule size from 340 to 250 μm. Inclusion of microcrystalline cellulose when alginic acid is present gives a much larger decrease from 415 to 250 μm. It seems likely that the type of packing in the powder bed is changed by the presence of the third component, giving different types of wet masses which give different granule sizes and distributions. The results on formulations granulated with water or by slugging are given in Tables 2 and 3. For OTC alone, granulation with water gave such weak granules that the reported mean granule size (92 μm) is dependent on the extent to which the granules were handled. Using water as the granulating liquid instead of a PVP solution does not appear to have much effect on the granule properties, apart from the strength being enhanced by the presence of PVP. For the tablets the dissolution time is reduced when any excipient is present, presumably due to the larger pores present in the tablet, and the effects of the disintegrants. Granules of OTC produced by slugging are radically different from those made by wet granulation: they are denser, with half the intragranular porosity and about 10% of the pore radius of granules produced by wet massing and screening. They are much stronger, which may be due to bond formation by a process of fusion of touching surfaces during compression.

Turning to the effects of microcrystalline cellulose and alginic acid on the properties of the OTC, the granule size distributions are shown in Figs 3 and 4. Granulation with water produced approximately the same effects on the distribution as granulation with PVP solution; slugging and breakdown naturally gave different distributions, with very much more fine material present. In all cases inclusion of the excipients reduced the mean granule size. As was the case with pure OTC the granules containing varying amounts of excipients were denser, less porous and much harder than those produced by wet granulation, which was due to the greater amount of compaction suffered by the powder bed when slugged.

The tablets prepared by compressing "slugged" granules always have lower disintegration times, and dissolution $T_{50\%}$ times than the same formulation prepared by wet

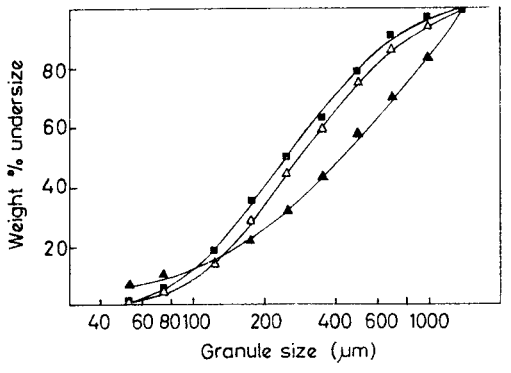

Fig. 3

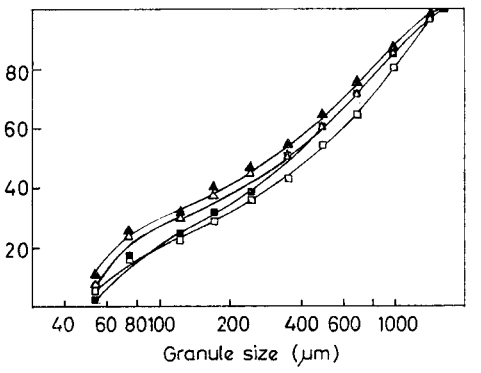

Fig. 4

FIG. 3. The granule size distributions of batches wet granulated with 30% v/w water. Excipient content: ▲ 2·7% w/w alginic acid, △ 7·2% w/w microcrystalline cellulose, ■ 2·7% w/w alginic acid and 7·2% w/w microcrystalline cellulose.

FIG. 4. The granule size distributions of batches prepared by slugging. Excipient content: □ 0% w/w, ▲ 2·7% w/w alginic acid, △ 7·2% w/w microcrystalline cellulose, ■ 2·7% w/w alginic acid and 7·2% w/w microcrystalline cellulose.

granulation (Tables 1 and 3). If we argue that to obtain the best possible disintegration, a tablet structure should have the disintegrant evenly distributed throughout its volume, so that water entering the structure through pores is continually able to contact the disintegrant as it passes through the tablet, by contrast an uneven distribution of disintegrant may leave areas of the tablet which represent restrictions for the entry of water. Slugging the powder mass as described fixes the individual particles in relation to one another as they are present in a good mix: i.e. within limits randomly distributed. The spatial relation between the powder particles formed into the granule can be altered in two main ways: rotation of the medium and large sized granules away from their original positions in relation to each other in the original "slug", and imposition between them of the very fine material.

With the true densities and mean particle size of the components of the formulation known, the relative number of particles can be calculated. In the formulation containing 2·7% w/w alginic acid, 96% of the particles are OTC, and 4% alginic acid. In that containing 7·2% microcrystalline cellulose, 22% are OTC and 78% are microcrystalline cellulose. Both microcrystalline cellulose and alginic acid are classed as disintegrants, and a comparison of the disintegration times for tablets made from "slugged" granulations, reveals large differences between them, in view of the differences in the relative numbers of particles present. The standard formulation contains 21% of OTC particles, 78% of microcrystalline cellulose, and 1% of alginic acid. With granules from the slugging process, these tablets explode when placed in water (Table 3).

When the wet granulation process is considered, a third mechanism for altering the spatial relation between the primary powder constituents of the granules becomes apparent. Powders with different amounts of hydrophobicity and different degrees of surface roughness will differ in their ability to take part in liquid bonding processes. Powder particles readily taking part in such processes are likely to be moved to new positions when contact with the aqueous medium is established. More hydrophobic particles will not enter so readily into the formation of liquid induced bonds. This can give rise to microscopic inhomogeneities due to the capillary forces. This additional inhomogeneity may explain why the tablet made from granules prepared by massing and screening are slower to disintegrate and dissolve than those prepared from "slugged" material (Table 3).

REFERENCE

CHALMERS, A. A. & ELWORTHY, P. H. (1976). *J. Pharm. Pharmac.*, **28**, 228–233.