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Some formulation factors affecting the tensile strength, disintegration and dissolution of uncoated oxytetracycline tablets

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A study has been made of the effects of gelatin binding agent and moisture content on the tensile strength, disintegration and dissolution times of oxytetracycline tablets. These properties all increase with the gelatin content, and maximum tensile strengths occur when the tablets contain between 2·5 and 4·5% w/w of moisture. The properties of the tablets depend on their packing fraction and in general, the disintegration and dissolution times are minimal when the packing fraction is between 0·77 and 0·82.

A connection has been established between the disintegration times of the tablets and the time required for 50% of the drug content to dissolve.

A typical formulation for commercial oxytetracycline tablets consists of (% w/w) oxytetracycline dihydrate 90·2, Avicel PH101 7·2, alginic acid HED 2·6, plus an appropriate quantity of an aqueous gelatin solution (Bloom No. 300, acid-treated-hide) to act as the binding agent (Esezobo & Pilpel, 1974).

The mixture is wet granulated through a No. 12 mesh sieve, dried, resieved through a No. 16 mesh sieve and is then compressed into 300 mg biconvex tablets containing approximately 250 mg of the active drug.

It can be inferred from previous work (Eriksson, 1964; Yen, 1964; Shotton & Rees, 1966; Sakr, Kassem & others, 1972; Davies & Gloor, 1972) that the properties of the tablets, such as their uniformity of weight, mechanical strength, disintegration and dissolution times will depend on the tableting conditions employed, on the size distribution of the granules and particularly on their content of moisture and gelatin binding agent. Thus Jacob & Plein (1968) and Sakr & others (1972) have shown that increasing the gelatin content of tablets caused increases in their mechanical strength and disintegration and dissolution times; Ganderton, Hadgraft & others (1967), Polderman & Braakman (1968), Smith, Baker & Wood (1971) and Khan & Rhodes (1972) showed that maxima or minima occurred when the disintegration and dissolution times of the tablets were plotted against their packing fraction.

Previously (Esezobo & Pilpel, 1974) we compressed an oxytetracycline formulation, containing various amounts of moisture and gelatin, into the form of beds and subjected these to shearing and tensile tests in an annular shear cell and a split plate tester (Kočova & Pilpel, 1971). We showed that increasing the moisture and gelatin content caused increases in the values of certain fundamental mechanical properties of the formulations (Pilpel 1971), such as their angle of internal friction and their cohesion and tensile strengths at the rather low packing fraction of 0·47.

Commercial oxytetracycline tablets normally have packing fractions in excess of 0·75 and it was therefore considered desirable to see to what extent the changes produced by moisture and gelatin on the mechanical properties of rather loosely

packed beds would be reflected in the properties of compacts and various types of tablets prepared from granules of the same formulations. This has been the purpose of the present work.

Compacts of 2·54 cm diameter and tablets of 1·03 cm diameter were prepared from the formulated granules in a hand press. Tensile strengths were measured by the diametral compression test (Fell & Newton, 1970), the disintegration times of the tablets by the Standard BP (1973) method and their dissolution times by the beaker method (Levy & Hayes, 1960).

MATERIALS AND METHODS

Preparation of granules

500 g batches of the formulation were mixed for 1·5 min in a small planetary mixer with 250 ml of distilled water containing different amounts of dissolved gelatin (Esezobo & Pilpel, 1974). The wet masses, which contained between 0 and 7·5% (w/w) of gelatin, were granulated through a No. 12 mesh sieve, the granules were dried at 50° for 18 h and then resieved through a No. 16 mesh sieve. Shorter drying periods were employed for samples which were required to contain more than 4·0% w/w moisture.

Preparation of compacts

Approximately 5 g of the granules were weighed into a stainless steel die, 2·54 cm in diameter, which rested on a horizontal steel plate. It was fitted with a close-fitting flat punch and the punch and die were lubricated by brushing on a 2% (w/v) dispersion of magnesium stearate (BDH Technical grade) in ether–ethanol (1 : 1).

The granules were compressed in the die by means of a hand operated press (Research and Industrial Instrument Co. London) applying predetermined loads for 2 min. The compacts were ejected and their weights and dimensions were then accurately measured to within ± 1 mg and $\pm 0{\cdot}01$ mm to give their packing fractions.

Preparation of tablets

For preparing tablets, 1% w/w magnesium stearate was added to the granules. A similar procedure was used for compressing them in standard 1·03 cm diameter punches and dies. Four types of tablet were made:—

Shape	*Total weight* (mg)	*Weight of oxytetracycline* (mg)
Flat faced	300 ± 10	250
Flat faced	600 ± 10	500
Deep biconvex	300 ± 10	250
Deep biconvex	600 ± 10	500

After ejection they were stored for 24 h to allow for hardening and elastic recovery and their weights and thicknesses were accurately measured before testing to obtain their packing fractions (weight/volume/particle density).*

Testing

The tensile strengths of the compacts and of the 300 and 600 mg flat-faced and the 600 mg biconvex tablets were measured using the diametral compression test (Fell &

* An appendix on the derivation of the packing is available on request to the Editorial Department of the Journal.

Newton, 1970) (it was not possible to use this test on the 300 mg biconvex tablets because they tended to cap as soon as they were placed in the apparatus). Standard padding strips (0·08 cm thick and 0·45 cm wide) were used in the tests to ensure even distribution of stress (York & Pilpel, 1973). The measurements were carried out in triplicate or more at an ambient R.H. of 50% and results were only taken from samples which split cleanly into two halves.

For the flat-faced specimens, the tensile strength, T, is

$$T = \frac{2P}{\pi Dt}$$

where P is the applied stress in MN, D is the compact/tablet diameter in cm, t is the compact/tablet thickness in cm and for the deep biconvex tablets

$$T = \frac{2P}{\pi(0{\cdot}283 + 1{\cdot}03\,(t - 0{\cdot}402))}$$

(Little & Mitchell, 1963; Esezobo, 1975).

The disintegration times of the 300 mg biconvex tablets were measured in distilled water at 37 $\pm$ 0·5° in a Manesty disintegration tester by the B.P. (1973) method.

Their dissolution rates were determined at the same temperature, using a round bottomed flask, stirring speed of 100 rev min^{-1}, 2 litres of a standard pH 2 buffer solution (B.P. 1973) and a spectrophotometric method (at an absorbance of 353 nm), for assaying the oxytetracycline (Hiscox, 1951) with a Cecil CE202 Spectrophotometer. All measurements were made in triplicate or more and the results given are the mean of several determinations.

RESULTS

Fig. 1 shows the connection between the amounts of gelatin employed in the formulations and the sizes and size distributions of the resulting granules. The higher the gelatin content the larger the granules and the wider their size distribution.

Fig. 2 is typical of the way in which the tensile strengths of the 2·54 cm diameter compacts varied with their moisture content and packing fraction. Similar families of curves were obtained when the gelatin content was increased incrementally from 0 to 7·5% (w/w), increasing the gelatin in all cases causing an increase in tensile strength.

Fig. 3 shows how the tensile strengths of these compacts at a particular packing fraction of 0·70 varied with their moisture and gelatin contents (similar results were obtained at other packing fractions). Initially the tensile strengths of the compacts increased with moisture content but at concentrations above 3–4% (w/w), they started to decrease.

Data on the tensile strengths of the various types of tablets are summarized in Table 1 and some typical results are plotted in Figs 4 and 5.

The results of the disintegration tests on the 300 mg biconvex tablets are plotted in Fig. 6.

Typical dissolution profiles for tablets compressed to different packing fractions, but all containing the same i.e. 3·75% (w/w) of gelatin are shown in Fig. 7. Fig. 8 illustrates how the values of t50% (i.e. the time required for 50% of the oxytetracycline to dissolve from these tablets) depended on their packing fractions and gelatin contents. Additional relevant data are given in Table 2.

Table 1. *Summarized tensile strengths at packing fraction = 0·85.*

Wt of granules used (mg)	Shape of tablets	Moisture content range (% w/w)	Concentration of gelatin (% w/w)	Log tensile strength (MN m^{-2})	Tensile strength (MN m^{-2})
600·0	Flat-faced	2·57–3·48	0	0·15	1·41
			2·50	0·26	1·82
			3·75	0·29	1·95
			5·00	0·36	2·29
			6·25	0·40	2·51
			7·50	0·46	2·88
300·0	Flat-faced	2·57–3·48	0	0·13	1·35
			2·50	0·20	1·56
			3·75	0·24	1·74
			5·00	0·32	2·09
			6·25	0·38	2·40
			7·50	0·44	2·75
600·0	Biconvex	2·57–3·48	0	0·05	1·12
			2·50	0·11	1·29
			3·75	0·21	1·62
			5·00	0·28	1·91
			6·25	0·33	2·14
			7·50	0·42	2·63

Fig. 9 shows the connection between the disintegration times and the dissolution (t50%) times when various amounts of gelatin were present in the tablets.

DISCUSSION

Although the variations in granule size shown in Fig. 1 might be expected to have some effect on the tensile strengths (Newitt & Conway-Jones, 1958; Rumpf, 1962; Shotton & Ganderton, 1961) and the disintegration and dissolution times (Levy, Antkowiak & others, 1963; Yen, 1964) of the compacts and tablets prepared in the present work, production batches of oxytetracycline granules always contain a range of sizes. It seems reasonable to assume that the effects of granule size on the tensile strengths, disintegration and dissolution times of the present compacts and tablets would be small in comparison with those caused by alterations in the packing fraction, moisture content and gelatin content of the formulation. The assumption is supported by the work of Higuchi, Rao & others (1953) on sulphathiazole and has recently been confirmed by comparing the tensile strengths of compacts made from different sized granules of oxytetracycline (Esezobo, thesis in preparation).

The present observation (Fig. 3) of an initial increase in the tensile strengths of the compacts followed by a decrease when the moisture concentration was raised above 3–4% (w/w), accords with results obtained by certain other workers (Shotton & Rees, 1966; Armstrong & Griffiths, 1970). But the results contrast with those from other work (Esezobo & Pilpel, 1974) in which smaller granules of the oxytetracycline formulation were compressed to a lower packing fraction of 0·47 in a split-plate tester.

It seems probable that at relatively low packing fractions, any moisture present is in the form of pendular, funicular or capillary bonds, whose contribution to the tensile strength of the mass can be expressed in quantitative terms (Rumpf, 1962; Pilpel 1969). However, at higher packing fractions the moisture, if present in sufficient quantity,

Table 2. *The influence of gelatin content and packing fraction on the dissolution of 300 mg (1·03 cm diameter) biconvex tablets and on disintegration at packing fraction = 0·80.*

Concentration of gelatin (% w/w)	Moisture content (% w/w)	Mean packing fraction (Pf)	t25% min	t50% min	t75% min	t50%min at Pf = 0·80	Disintegration time (min) at Pf = 0·80
		0·734	1·25	2·50	5·50		
		0·807	1·00	2·00	3·50		
0	3·09	0·856	1·00	1·75	2·50	1·85	1·30
		0·871	1·00	2·00	3·40		
		0·920	2·00	4·00	8·25		
		0·722	2·00	3·63	5·50		
		0·797	1·50	2·63	4·63		
2·50	2·96	0·809	1·75	2·75	3·38	2·75	1·60
		0·850	1·63	3·00	5·25		
		0·876	2·88	5·25	8·75		
		0·694	8·00	16·50	34·00		
		0·778	5·25	9·00	15·75		
3·75	3·48	0·840	8·50	14·00	25·50	9·90	7·00
		0·864	13·75	20·50	29·25		
		0·900	17·75	32·50	52·50		
		0·696	14·00	38·00	132·00		
5·00	2·72	0·788	15·50	30·00	76·50	48·00	20·90
		0·833	55·00	110·00	180·00		
		0·859	74·00	152·00	a		
		0·693	27·50	77·00	b		
6·25	2·57	0·782	36·00	90·00	c	120·0	56·00
		0·830	67·00	182·00	d		

a = 65% Released after 180 min. b = 67·5% Released after 180 min. c = 71·0% Released after 180 min. d = 57·0% Released after 210 min.

begins to act as a lubricant or dispersion medium, reducing the cohesive forces between the particles and hence, the tensile strength of the mass (Derjaguin, 1961). This occurs when more than 3 to 4% (w/w) of water is present. The effect depends also on the gelatin content.

The tablets listed in Table 1 had water contents between 2·6 and 3·5% (w/w) and they were therefore probably the "strongest" that could be prepared at the particular packing fraction of 0·85 employed.

As expected from previous work (Esezobo & Pilpel, 1974) and from the present results on the compacts, Figs 2 and 3, the tensile strengths of the tablets increased with their packing fraction and gelatin content. It is seen from Fig. 5 that the flat faced tablets had slightly higher tensile strengths than the biconvex tablets of the same weight and this finding agrees with results for starch/lactose tablets reported by Munzel & Seth (1960). The figure also shows that (for the flat faced tablets) the 600 mg tablets had higher tensile strengths than the 300 mg tablets.

Turning next to the disintegration and dissolution results, Figs 6 and 8 show that as the packing fraction was increased, there was initially a decrease in both the disintegra-

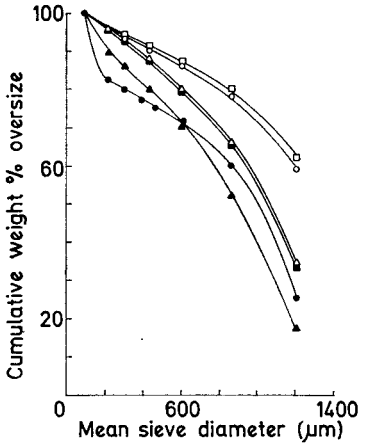

FIG. 1.

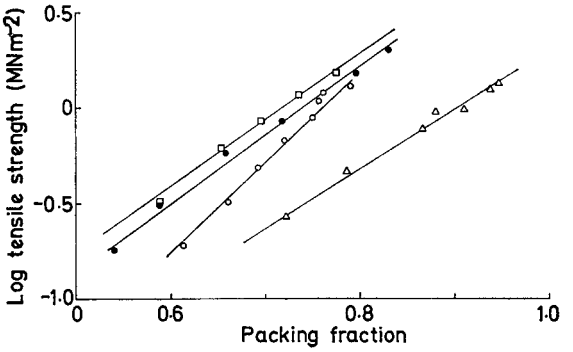

FIG. 2.

FIG. 1. Sieve analysis of oxytetracycline granules. Gelatin (% w/w): ● 0, ▲ 2·5, ■ 3·75, △ 5·0, □ 6·25, ○ 7·5.

FIG. 2. Effect of moisture on log tensile strength *vs* packing fraction of oxytetracycline compacts containing 5·0% w/w gelatin. Moisture (% w/w): ○ 2·6, □ 3·7, ● 5·5, △ 7·6.

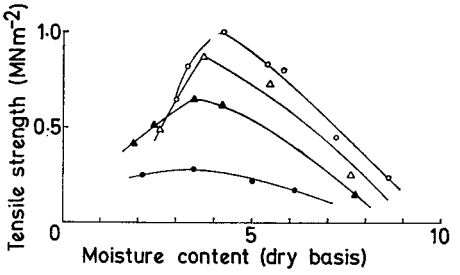

FIG. 3.

FIG. 3. Effect of moisture and gelatin content on tensile strengths of oxytetracycline compacts at packing fraction = 0·70. Gelatin (% w/w): ● 0, ▲ 2·5, △ 5·0, ○ 7·5.

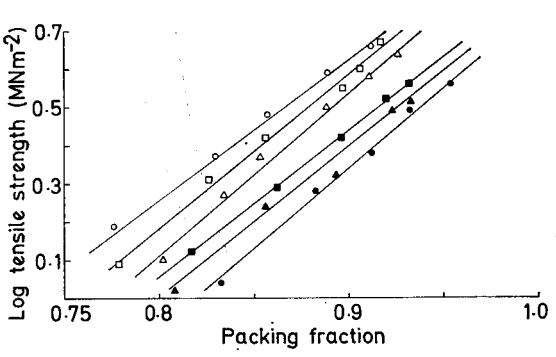

FIG. 4.

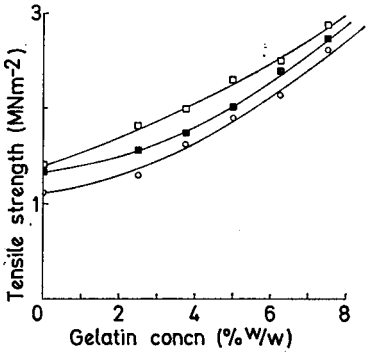

FIG. 5.

FIG. 4. Effect of gelatin content on log tensile strength *vs* packing fraction of 300 mg 1·03 cm diameter flat faced tablets at approximately constant moisture content. Gelatin (% w/w): ● 0, ▲ 2·50, ■ 3·75, △ 5·00, □ 6·25, ○ 7·50. Moisture (% w/w): ● 3·1, ▲ 3·0, ■ 3·5, △ 2·7, □ 2·6, ○ 2·6.

FIG. 5. Effect of gelatin content on the tensile strengths of three types of tablets at packing fraction = 0·85 and at moisture contents of between 2·6–3·5% w/w. □ Flat faced 600 mg tablets. ■ Flat faced 300 mg tablets. ○ Biconvex 600 mg tablets.

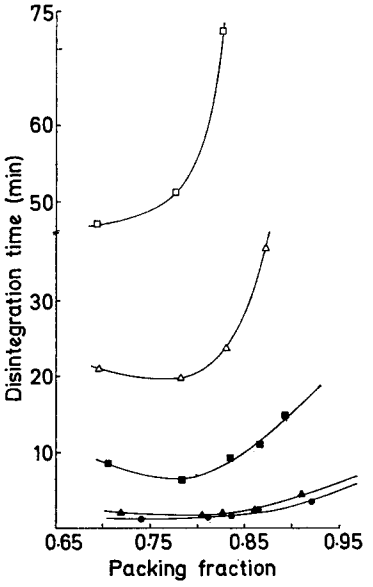

FIG. 6.

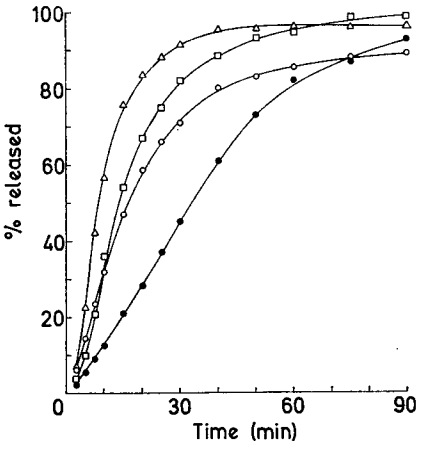

FIG. 7.

FIG. 6. The combined effects of gelatin content and packing fraction on the disintegration of 300 mg 1·03 cm diameter biconvex tablets. Gelatin (% w/w): ● 0, ▲ 2·5, ■ 3·75, △ 5·0, □ 6·25.

FIG. 7. The effect of packing fraction on dissolution of 300 mg 1·03 cm diameter biconvex tablets containing 3·75% w/w gelatin. Packing fractions: ○ 0·694, △ 0·778, □ 0·840, ● 0·900.

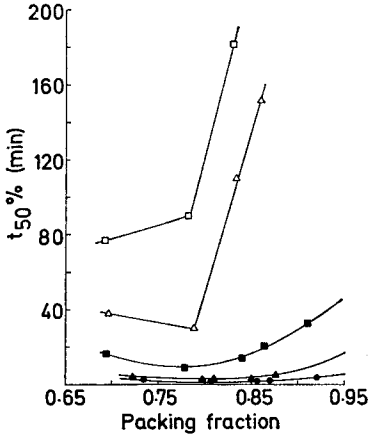

FIG. 8.

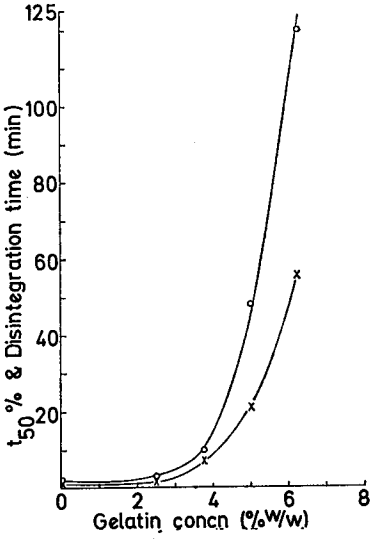

FIG. 9.

FIG. 8. The combined effects of gelatin content and packing fraction on the time for 50% dissolution of 300 mg 1·03 cm diameter biconvex tablets. Key as in Fig. 6.

FIG. 9. The effect of gelatin content on the disintegration and dissolution of 300 mg 1·03 cm diameter biconvex tablets at packing fraction = 0·80. × Disintegration test. ○ Dissolution test (t_{50}% min).

tion and dissolution (t50%) times, but that at higher packing fractions above (0·80) both increased.

The presence of small amounts (less than 3% w/w) of gelatin in the tablets had little effect on the results at any packing fraction, but with more gelatin (up to 6% w/w) the disintegration and dissolution times increased considerably, particularly as the packing fraction approached a value of 1·0.

Several other workers (Higuchi & others, 1953; Levy & others 1963; Polderman & Braakman, 1968; Smith & others, 1971) have reported on the occurrence of minima in disintegration and dissolution graphs of the type shown in Figs 6 and 8.

One explanation is that when granules are compressed in a die they fragment. This leads initially to an increase in their specific surface area, which has actually been detected by, for example, gas adsorption and Coulter counting techniques (Higuchi & others 1973; Armstrong & Griffiths, 1970; Rubinstein & Bodey, 1974). At higher pressures, these fragments presumably reform into compacts by processes of cold bonding between the particles (York & Pilpel, 1972) and this leads to the observed increases in disintegration and dissolution times.

An alternative explanation (Berry & Ridout, 1950; Khan & Rhodes, 1975) is that at low packing fractions, the present excipients Avicel, alginic acid and possibly gelatin, have sufficient space within the tablets to swell and dissolve without completely disrupting them, but that at packing fractions corresponding to the minima in Figs 6 and 8, the pore space is too small to accommodate the swollen particles, so that disruption occurs more rapidly. At still higher packing fractions, the rate at which liquid is able to penetrate the tablets is reduced and the disintegration and dissolution times therefore again increase.

The minima disappear when more than about 5% (w/w) of gelatin is present in the tablets (see also Polderman & Braakman, 1968) and this is presumably because the granules are now quite hard and thus only start to fragment with subsequent formation of new bonds, at high applied pressures.

Fig. 9 (which is confirmed by other published results, Yen, 1964; Polderman & Braakman, 1968; Smith & others, 1971) shows that the addition of gelatin beyond the 3% (w/w) concentration produced more or less parallel increases in both the disintegration and dissolution times of the tablets and these increases can be compared with those produced in the hardness of the tablets as measured by their tensile strengths Fig. 5.

Finally, if the time required for 50% of the active ingredient to dissolve is compared with the disintegration time, it is found that the former is approximately twice the latter at all the gelatin concentrations investigated.

CONCLUSIONS

The optimum tensile strength of oxytetracycline tablets is achieved when the granules contain between 2·5 and 4·5% w/w of moisture.

Flat faced tablets have slightly higher tensile strengths than deep biconvex tablets compressed to the same packing fraction.

The tensile strengths, disintegration and disolution times of the tablets increase with their gelatin content. The disintegration and dissolution times generally exhibit minima when the packing fraction is between 0·77 and 0·82.

There is a relation between the time required for 50% dissolution of the tablets and their disintegration.

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