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Moisture and gelatin effects on the interparticle attractive forces and the compression behaviour of oxytetracycline formulations

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The tensile strengths of compacts and/or tablets of the individual components and of granules prepared from an oxytetracycline formulation have been measured using the diametral compression test. Employing the theory of tensile strength, proposed by Cheng, it has been shown that increases in both moisture and gelatin contents of compacts and tablets increase the range of the attractive forces that operate between the granules. By studying the effects of moisture and gelatin on the compressional behaviour of the granules, it has been possible to classify them into different types. Fragmentation of granules occurs at packing fractions between 0·745 and 0·835, depending on their gelatin content.

Measurements of the tensile strengths of compressed powders and/or granules are widely used for providing basic information on the materials employed in the preparation of pharmaceutical tablets (Newton Rowley & others 1971; Ridgway, Lazarou & Thorpe 1972; Esezobo & Pilpel 1974, 1976).

Cheng (1968) derived an equation for estimating the average interparticle attractive forces, t_o, from tensile strength data obtained on relatively loosely packed powder beds. The equation incorporates the effects of density and particle size distribution and explains the large changes in tensile strength that occur when a small increase is made in the powder's packing fraction. This effect is ascribed to the occurrence of micro-contacts between asperities on the surfaces of the particles. In the present work, Cheng's equation has been applied to tensile strength results obtained on compacts and tablets by subjecting these to diametral compression tests.

Besides measuring the mechanical strengths of the compacts and tablets, we have also investigated how the densities of the constituent powders/granules varied with applied pressure. Many workers (Heckel, 1961; Cooper & Eaton 1962; Hersey & Rees, 1970, 1971; Fell & Newton 1971; Hersey, Rees & Cole, 1973; York & Pilpel, 1973) have proposed that consolidation of a powder or granular material takes place by the following mechanisms:

(i) At relatively low pressures, rearrangement of particles leads to closer packing, the energy being dissipated mainly in overcoming interparticle friction.

(ii) At higher pressures, elastic or plastic deformation of particles may occur, causing particles to fill the void spaces and thus increase the area of interparticle contact. For materials of low thermal conductivity and low melting point (e.g. gelatin) the frictional heat generated at points of contact may cause a rise in temperature, resulting in increased plasticity or even in melting (York & Pilpel, 1973).

(iii) Brittle powders or granules may fracture and rearrangement of the fragments leads to an increase in packing fraction.

The mechanisms may occur sequentially or simultaneously. The order in which they occur and their relative importance depend on the properties of the material and on the speed of compression.

We have studied the compression of mixed sizes of oxytetracycline granules, containing the following ingredients: oxytetracycline dihydrate, Avicel, alginic acid plus appropriate amounts of gelatin and moisture. The granules were formed into compacts and tablets and the tensile strengths of these measured. By analysing the results in terms of the equations of Cheng (1968), Heckel (1961) and Cooper & Eaton (1962) it was hoped (a) to establish whether the equations were valid for mixtures of materials, as well as for narrow size fractions of single substances. (see Kawakita & Lüdde, 1970/71; Kočova & Pilpel, 1973; York & Pilpel, 1973) and (b) to determine the effect of two of the compositional variables, moisture and gelatin content, on the compressional characteristics of the formulations (see Shotton & Rees, 1966; Armstrong & Griffiths, 1970; Cole, Elworthy & Sucker, 1975).

MATERIALS AND METHODS

Materials

The materials used were: oxytetracycline dihydrate B.P. (ICI Pharmaceutical Division), Avicel PH101

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(Honeywell and Stein, Limited), alginic acid HED (Alginate Industries Limited) and gelatin (Bloom No. 300, acid-treated hide from Richard Hodgson Limited). The oxytetracycline was dried at 60° for 24 h (it decomposed at higher temperatures) and the other materials were dried at 100°. They were stored in screw cap jars and their relevant physical properties have been given previously (Esezobo & Pilpel, 1974).

Preparation of formulation and granules

A standard oxytetracycline formulation was prepared by intimately mixing the dried powders for 15 min in a cylindrical jar in the following proportions (% w/w) oxytetracycline dihydrate 90·2, Avicel PH101 7·2, and alginic acid HED 2·6. The formulation was wet granulated through a No. 12 mesh sieve using different concentrations of aqueous gelatin solution as the binder, then dried and resieved through a No. 16 mesh sieve (Esezobo & Pilpel, 1974, 1976). The moisture contents of the final granules were controlled by drying for varying periods at 60°.

Preparation of compacts and tablets

5 g samples of the excipients, of the formulated mixture and of granules containing different amounts of gelatin and moisture were compressed under standard conditions (Esezobo & Pilpel, 1976) in a hydraulic press to form 2·54 cm diameter flat-faced compacts. The dried granules (to which had been added 1 % (w/w) magnesium stearate as a lubricant) were also formed into 600 mg deep biconvex tablets, 1·03 cm in diameter (Esezobo & Pilpel, 1976). The packing fractions of the finished compacts and tablets were determined in triplicate and quintuplicate respectively from their measured weights and dimensions.

Tensile strengths

These were measured by diametral compression employing the same equations for the calculation as in previous papers (York & Pilpel, 1973; Esezobo & Pilpel, 1976).

RESULTS

Fig. 1 shows the size distribution of the granules employed. The results of the diametral compression tests on the excipients and formulation are shown in Fig. 2 as plots of log tensile strength against packing fraction. The graphs are rectilinear and the results are similar to those obtained previously on loosely packed beds of the powders (Esezobo & Pilpel, 1974).

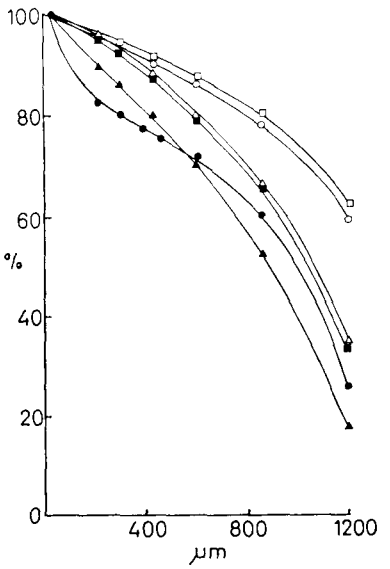

FIG. 1. Sieve analysis of oxytetracycline granules (μm). Gelatin (% w/w): ● 0, ▲ 2·5, ■ 3·75, △ 5·0, □ 6·25, ○ 7·5. y axis—Cumulative weight % oversize.

Cheng's (1968) expression for the tensile strength, T, of a dry powder bed or compact is:

$$T = abc\,\tfrac{1}{2}\left(\frac{\bar{s}}{\bar{v}}Pf\right)h\left(t_0 - \frac{\bar{d}}{3}\left[\frac{Pf}{Pf_0} - 1\right]\right) \quad (1)$$

(for definition see footnote)

Because some of the terms were originally derived on a number basis, it was now necessary to convert the sieve analysis data of the granules into cumulative

List of symbols used in equation (1): a = ratio of number of granule-pairs per unit area to the same per unit volume. b = ratio of overall area of contact per granule-pair to the surface area of the smaller granule of the granule-pair. c = coordination number. $\bar{d}$ = mean effective diameter of the granules. h(t) = interparticle force per unit overall area of contact. $\bar{s}$ = mean effective surface area per granule. t = surface separation of granules in the pair. t_0 = 'length' parameter of the interparticle attractive force. $\bar{v}$ = mean effective volume per granule. T = tensile strength per unit area. Pf = packing fraction of compact. Pf_0 = packing fraction when tensile strength is zero.

The equations for calculating the granule size parameters $\bar{d}$, $\bar{s}$ and $\bar{v}$ are as follows:

$$\bar{d} = \Sigma\, x_{ij}\,\tfrac{1}{2}\left[\tfrac{1}{2}(d_i + d_{i+1}) + \tfrac{1}{2}(d_j + d_{j+1})\right]$$
$$\bar{s} = \Sigma\, x_{ij}\,\tfrac{1}{2}(d_i + d_{i+1})^2 \quad (4)$$
$$\bar{v} = \Sigma\, \tfrac{\pi}{6}\, n_i\,\tfrac{1}{2}(d_i + d_{i+1})^3$$

where d_i, d_j = equivalent spherical diameters of granules; n_i = fractional number of granules between size d_i and d_{i+1}; x_{ij} = fractional number of granule pairs consisting of granules of sizes d_i and d_j.

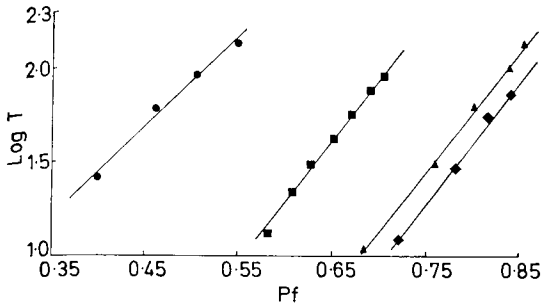

FIG. 2. Log tensile strength (T, $Nm^{-2} \times 10^{-4}$) *vs* packing fraction (Pf) for compacts of excipients and oxytetracycline formulation:

	(% w/w) moisture content
● Avicel	3·3
■ Alginic acid	5·2
◆ Oxytetracycline dihydrate	2·4
▲ Oxytetracycline formulation	2·8

number percentages by employing the Hatch-Choate equation (Edmunson, 1967) i.e.:

$$\ln dgn = \ln dgw + (\emptyset - 3) \ln^2 \sigma g \quad .. \quad (2)$$

(where dgn is the geometric mean diameter (number), dgw is the geometric mean diameter (weight), Ø is the Hatch-Choate coefficient and σg is the geometric standard deviation). Plotting the results on a log-probability graph yields Fig. 3. The resulting granule size distribution (number basis), was then substituted into equation (4) footnote to obtain the size parameters $\bar{d}$, $\bar{s}$ and $\bar{v}$ which are listed in Table 1. These

Table 1. *Granule size parameters $\bar{d}$, $\bar{s}$ and $\bar{v}$ used in Equation 1.*

	% (w/w) gelatin content					
	0	2·50	3·75	5·00	6·25	7·50
$\bar{d}$ (μm)	246·2	273·2	250·7	232·4	263·2	265·7
$\bar{s} \times 10^{-5}$ (μm)²	1·8	2·1	1·8	1·5	0·62	0·81
$\bar{v} \times 10^{-8}$ (μm)³	8·8	13·8	7·4	5·7	0·76	1·3

values together with the values of tensile strength and of Pf_0 i.e. the packing fraction when the tensile strength is zero (obtained by extrapolating the tensile strength versus packing fraction curves to T = O) were used to calculate the functions

$$\frac{1}{\bar{F}} \text{ and } \frac{\bar{d}}{\bar{s}}\left(\frac{Pf}{Pf_0} - 1\right), \left[\text{where } \frac{1}{\bar{F}} = \left(\frac{\frac{1}{2}\frac{\bar{s}}{\bar{v}} Pf}{T}\right)\right].$$

A representative graph of $\frac{1}{\bar{F}}$ versus $\frac{\bar{d}}{\bar{s}}\left(\frac{Pf}{Pf_0} - 1\right)$ for

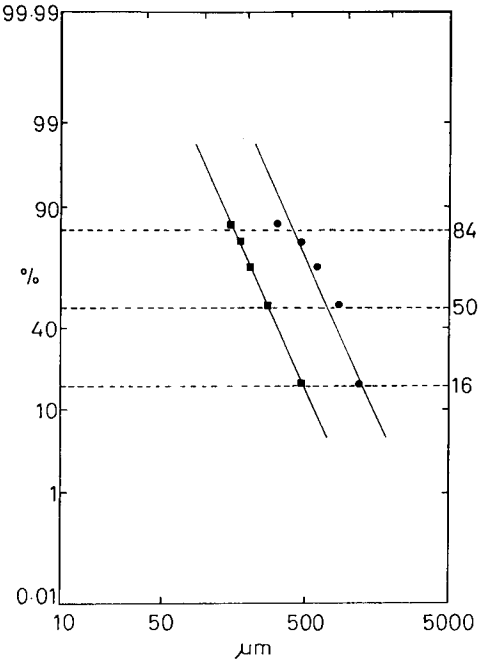

FIG. 3. Log-probability graphs of granules containing 2·5% (w/w) gelatin. ● Weight basis ■ Number basis. y axis—Cumulative weight % oversize (on probability scale). x axis—Mean sieve diameter (μm) (on log scale).

the 600 mg biconvex tablets containing different amounts of gelatin is shown in Fig. 4. (Similar graphs were obtained for tablets containing different levels of moisture.)

It is seen, Fig. 4, that instead of the continuous straight lines usually obtained with this type of plot on loosely packed beds or compacts of powders (see York, 1973), there are abrupt changes in slope and all the graphs show two distinct regions. In order to obtain the values of $t_0\left[= t + \frac{\bar{d}}{\bar{s}}\left(\frac{Pf}{Pf_0} - 1\right)\right]$ the two slopes were extrapolated independently to 1/F equals zero, and although they refer to the tensile strength at zero load for two different states of the compacts, $t_{o\ mean}$ was conveniently taken as

$(t_{0_1} + t_{0_2})/2$.

The graph of $t_{o\ mean}$ versus % (w/w) gelatin content for the 600 mg tablets is plotted in Fig. 5 and shows that $t_{o\ mean}$ increases with increase in gelatin content. The figure also shows that it increases with moisture content.

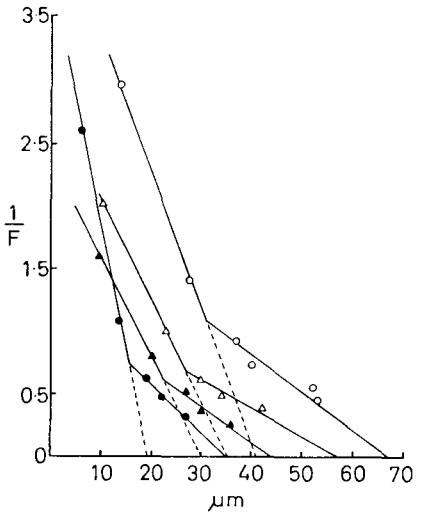

FIG. 4. Relation between $\frac{1}{F}$ ($N^{-1}m$) and $\frac{\bar{d}}{3}\left(\frac{Pf}{Pf_0}-1\right)$($\mu$m) for 600 mg biconvex tablets. [Moisture content 2·6–3·5% (w/w)]. Gelatin % (w/w). ● 0, ▲ 2·5, △ 5·0, ○ 7·5.

The pressure/density relationships for the various materials were next analysed using the Heckel (1961) equation (An attempt to analyse the compression data from the oxytetracycline granules using the Cooper & Eaton (1962) equation failed.) The Heckel equation is:

$$\ln\left(\frac{1}{1-Pf}\right) = k\pi + A \quad .. \quad .. \quad .. \quad (3)$$

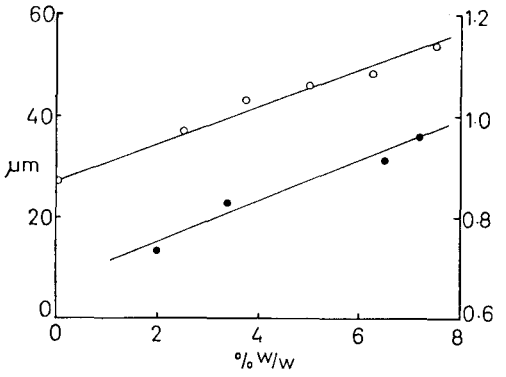

FIG. 5. Effects of gelatin and moisture on $t_{0\ mean}$ (μm) for 600 mg biconvex tablets and 5 g compacts. ○ Gelatin effect on tablets prepared from unmilled granules represented by LH ordinate. ● Moisture effect on compacts prepared from milled granules represented by RH ordinate. x axis—Moisture and gelatin contents (% w/w).

where Pf is the packing fraction of compacts or tablets, k, A are constants and are obtained from the slope and the intercept respectively of the extrapolated linear region of a plot of ln (1/1–Pf) *vs* π. π is the applied pressure.

Fig. 6 shows the Heckel plots for the powdered excipients and for the oxytetracycline formulation

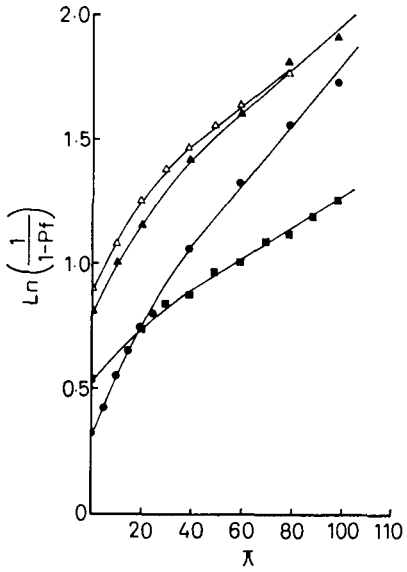

FIG. 6. Ln $\frac{1}{(1-Pf)}$ *vs* compressive stress (π) (MN m^{-2}) for the excipients and oxytetracycline formulation.

	k × 10^2 $(MNm^{-2})^{-1}$
● Avicel	1·22
■ Alginic acid	0·61
△ Oxytetracycline dihydrate	0·80
▲ Oxytetracycline formulation	0·87

while Figs 7 (a, b) and 8 are similar plots for representative granules containing different amounts of moisture and gelatin. Table 2 gives the values of various parameters which are derived from the Heckel equation and also includes the values of the constants, A and k.

Finally, Table 3 lists the packing fractions at the points where the curved and the linear regions in Fig. 8 intersect and those at which breaks occur in the graphs shown in Fig. 4.

DISCUSSION

Bearing in mind the unavoidable slight differences in the particle sizes and moisture contents of the excipients and formulation, it can be seen (Fig. 2) that at any packing fraction, the Avicel compacts have the highest tensile strength, followed by those of alginic acid, the oxytetracycline formulation and

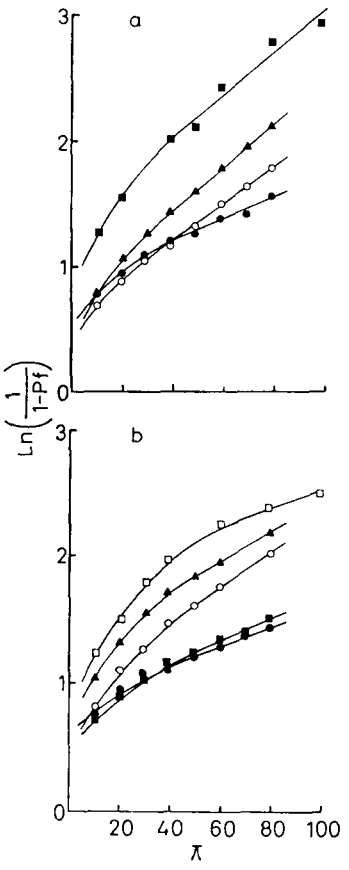

FIG. 7. Effect of moisture content on graphs of ln $1/(1 - Pf)$ *vs* compressive stress (π)(MNm^{-2}) for compacts. a. 5·0% (w/w) gelatin % (w/w) moisture content: ● 2·6, ○ 3·7, ▲ 5·5, ■ 7·6.

b. 7·5% (w/w) gelatin % (w/w) moisture content: ● 3·0, ■ 4·3, ○ 5·8, ▲ 7·2, □ 8·6.

pure oxytetracycline dihydrate. This pattern is the same as that obtained on relatively loosely packed beds of these materials (Esezobo & Pilpel, 1974).

It was observed that when compression pressures greater than about 70 MNm^{-2} were used for preparing compacts, those made from oxytetracycline powder alone tended to cap or laminate but those made from the formulation did not. Thus, the excipients, Avicel in particular and alginic acid to a lesser extent, appear to counteract the elastic recovery of pure oxytetracycline after compression and thus reduce its tendency to lamination and capping, This explains, in part, their incorporation in the formulation and it is clear that by altering the amounts and proportions of these two excipients, one should, to some extent, be able to control the strengths of the compacts (or tablets).

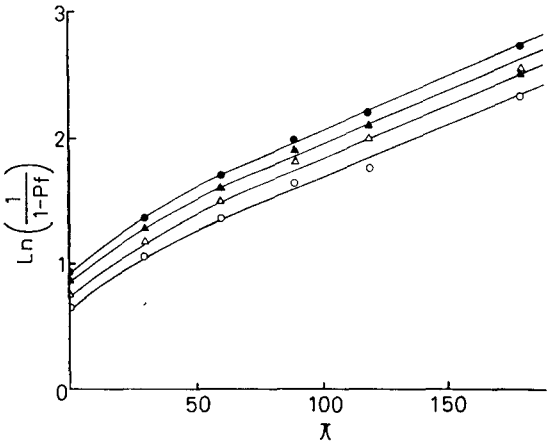

FIG. 8. Effect of gelatin content on graphs of ln $1/(1 - Pf)$ *vs* compressive stress (π) (MNm^{-2}) for 600 mg biconvex tablets. [Moisture content 2·6–3·5% w/w]. Gelatin % (w/w): ● 0, ▲ 2·5, △ 5·0, ○ 7·5.

Although Fell & Newton (1970) and York & Pilpel (1973) suggested that it might be possible to make quantitative predictions of the tensile strengths of tablets (prepared by direct compression of simple powder mixtures) from those of the individual components, this now appears less likely if the formulation contains several different components

Table 2. *Derived parameters obtained on the granules using Equation 3.*

Gelatin (w/w)	Moisture (w/w)	Pf_{OH}	Pf_A	Pf_B	$k \times 10^3$ $(MNm^{-2})^{-1}$	A	Cal. Pf at break
(A) Compacts—effects of moisture content.							
0	2·1	0·429	0·617	0·188	0·84	0·94	0·688
	3·5	0·468	0·593	0·125	1·20	0·90	0·717
	5·0	0·537	0·624	0·087	1·40	0·98	0·742
	6·1	0·559	0·756	0·197	1·40	1·42	0·865
2·50	1·8	0·412	0·585	0·173	0·82	0·86	0·697
	2·4	0·450	0·585	0·135	0·95	0·87	0·684
	3·4	0·485	0·567	0·082	1·40	0·80	0·703
	4·2	0·441	0·573	0·132	1·36	0·84	0·704
	7·7	0·601	0·777	0·176	1·48	1·50	0·869
5·0	2·6	0·451	0·576	0·126	0·88	0·86	0·693
	3·7	0·338	0·462	0·124	1·51	0·60	0·696
	5·5	0·329	0·524	0·195	1·73	0·74	0·718
	7·6	0·588	0·744	0·156	1·68	1·36	0·867
7·50	[3·0]	0·462	0·573	0·111	0·76	0·83	0·677
	4·3	0·383	0·563	0·180	0·86	0·82	0·690
	5·8	0·405	0·602	0·197	1·36	0·94	0·769
	7·2	0·512	0·717	0·205	1·20	1·24	0·821
	8·6	0·567	0·835	0·268	0·74	1·80	0·895
(B) Biconvex tablets-effect of gelatin at approximately constant moisture level							
0		0·608	0·699	0·091	0·842	1·20	0·815
2·5		0·585	0·667	0·082	0·821	1·10	0·798
3·75	2·6–	0·559	0·650	0·091	0·821	1·06	0·801
5·00	3·5	0·533	0·631	0·098	0·821	1·00	0·780
6·25		0·507	0·617	0·110	0·821	0·94	0·767
7·50		0·474	0·576	0·102	0·821	0·86	0·745

Table 3. *Effect of gelatin content on the packing fraction at which fragmentation of granules occurred.*

Gelatin content % (w/w)	Values of packing fraction (Pf) at which breaks occurred in Figs 4 and 8 using: Cheng equation	Heckel equation
0	0·835	0·815
2·50	0·818	0·798
3·75	0·834	0·801
5·00	0·825	0·780
6·25	0·791	0·767
7·50	0·767	0·745

and it has been wet granulated (Cook, Hone & Newton, 1975; Kurup & Pilpel, 1976).

It may be seen from Fig. 5, that the average interparticle attractive force, $t_{o\ mean}$, increased with increase in the gelatin content and this is as expected since a binding agent increases interparticle cohesion. The gelatin may also increase the roughness of the particles when present on their sufaces. The $t_{o\ mean}$ values obtained (Fig. 5) are about 30 times higher than those obtained for similar tablets prepared from powder or milled granules (Esezobo, 1976) probably due to the larger size of granules employed. Cheng (1968), stated that the size parameters of a material are of prime importance in determining the magnitude of $t_{o\ mean}$. Similarly, an increase in moisture content also resulted in an increase in the values of $t_{o\ mean}$ for the tablets prepared from the granules (Fig. 5). The average interparticle attractive forces in dry powders are non-specific and are essentially van der Waals' forces. But an additional attractive force due to surface tension will arise if moisture is present (Esezobo & Pilpel, 1974, 1976).

In the derivation of equation (3), Heckel (1961) considered that the reduction in voidage of a powder with compression obeyed a first-order kinetic relationship and the plots of $\ln(1/1-Pf)$ *vs* π produced graphs with an initial curved region, followed by a linear region as obtained in Figs 6, 7 (a, b) and 8. The curved region is due to particle or granule movement while the linear region occurs when densification is proportional to the void fraction. This corresponds to plastic deformation and cold-working with or without fragmentation. Thus, the constant, A, represents the degree of packing achieved at low pressures as a result of rearrangement processes before appreciable amounts of interparticle bonding takes place. The second constant, k, represented by the linear region, depends on the material involved, For example, Heckel (1961), showed that soft ductile powders have higher k values than hard powders. Similarly, oxides within powder particles and in the form of surface films reduce the values of k and high values indicate the onset of plastic deformation at relatively low pressures.

On the basis of the Heckel equation, Hersey & Rees (1970) and York & Pilpel (1973) have classified powders into three types (referred to as Types A, B and C) depending on their compaction behaviour. Types A and B are obtained from different particle size fractions of the powders. With Type A materials (e.g. sodium chloride) a linear relation is observed at all applied pressures indicating that sodium chloride deforms apparently only by plastic deformation, while for Type B (e.g. lactose) there are initial curved regions followed by parallel straight lines. This indicates that the particles are fragmenting at an early stage of the compaction process. For Type C materials (e.g. lauric, palmitic and stearic acids) the initial linear regions for the individual fatty acids become superimposed and flatten out as the applied pressure is increased. This is ascribed (York & Pilpel, 1973) to the absence of a rearrangement stage and densification is due to plastic deformation and asperity melting.

It is seen in Fig. 6 that the Avicel has the highest value of k followed by the oxytetracycline formulation, the pure oxytetracycline and the alginic acid powder. The result indicates that the Avicel is the softest and most easily compressible while the pure oxytetracycline and alginic acid powders are comparatively harder and more difficult to compress into compacts.

The graphs for the compacts and tablets containing different levels of moisture and gelatin, Fig. 7 (a, b) and 8 show initial curved portions followed by parallel straight lines for pressures above 30 and 50 MNm^{-2} respectively. Thus, all the formulated oxytetracycline granules behaved as Type B materials (Hersey & Rees, 1970, 1973; York & Pilpel, 1973). These granules had essentially the same particle size distributions, (slight differences being due to their different gelatin contents), and thus, the Type B behaviour must be due to the combined effects of moisture and binding agent and not in these systems to differences in particle size.

It is seen from Table 2A that increase in moisture content, at a fixed gelatin content, resulted in an increase in the values of the constants A and k, indicating a greater degree of densification at low pressures and improved compressibility of the materials as their moisture contents increased. In contrast, Table 2B shows that both A and k more

or less decrease with increase in gelatin at approximately constant moisture level. The change in k indicates that the granules become harder, the change in A that there is a reduction in the degree of densification at low pressures as the gelatin content is increased.

Various workers (e.g. Higuchi, Rao & others, 1953; Armstrong & Griffiths 1970; Carless & Sheak, 1976) using other methods have shown that fragmentation of granules occurs when these are compressed to high packing fractions. Although from the pressure/density studies on powders, it has not been possible in practice to demonstrate precisely when the mechanism of consolidation changes, since the stages of packing and deformation may occur concurrently, it is reasonable to assume that rearrangement and fragmentation of the oxytetracycline granules is occurring before plastic deformation of the constituent particles (i.e. at the point of intersection of the curved and linear regions in Fig. 8). The values in columns 2 and 3 of Table 3 compare satisfactorily over the whole range of gelatin content, granules containing small amounts of gelatin having to be compressed to high packing fractions before they fragment. Furthermore, the values in the Table correspond to the range of packing fractions at which oxytetracycline tablets exhibit minima in their disintegration and dissolution times (Esezobo & Pilpel, 1976).

CONCLUSIONS

The results of the tensile strength measurements on compacts and tablets obtained in this investigation, lead to similar conclusions to those for loosely packed beds of the same materials.

The Cheng equation has been successfully applied to compacts and tablets of oxytetracycline and the values of the mean range of attractive interparticle forces, $t_{o\ mean}$, have been shown to increase with increase in both moisture and gelatin concentration.

Changes in moisture and gelatin content produce compression behaviour similar to that shown by Type B materials.

Using two different approaches, it has been shown that fragmentation of oxytetracycline granules (having the size distributions shown in Fig. 1) takes place between packing fractions of 0·745 and 0·835 depending on the amount of gelatin present in the formulation.

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