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Fundamental properties of metronidazole formulations in relation to tableting

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A study has been made of the effects of polyvinylpyrrolidone, gelatin and methylcellulose binding agents on the fundamental and tableting properties of a metronidazole-lactose-starch formulation. A material constant, α, was derived from the measured values of tensile strength of the materials. The values of α for the formulations are lower than that for metronidazole and depend on the nature and concentration of binder present. In terms of tableting properties, α supplements the information obtained from the ratios of elastic recovery to plastic compression (ER/PC) and from the brittle fracture index values (BFI) of the materials, although its influence appears to be limited at low values of ER/PC.

Metronidazole is produced commercially in the form of tablets containing between 40 and 60% w/w of excipients (Martindale 1982). These modify its fundamental mechanical properties and reduce lamination and capping of its tablets (Itiola & Pilpel 1986a).

In the present work, measured values of the tensile strengths of metronidazole formulations have been used to obtain values of a quantity α (from the equations of Cheng 1968; Chan et al 1983). The work of these authors using single materials leads to the belief that α is also likely to be a constant for each formulation and a measure of the 'strength' and 'range' of forces acting between its particles. The objectives of the work have been to see how the type and amount of binding agent used in a formulation alter its value of α and also whether there is any correlation between the values of α and the tableting properties of the formulations.

Theory. Cheng's (1968) equation for the tensile strength, T, of a packed bed of powder is written as

$$T = \tfrac{1}{2}abc\,\frac{\bar{s}}{\bar{v}}\,P_f\,H\left[t_o - \frac{\bar{d}}{3}\left(\frac{P_f}{P_{f_0}} - 1\right)\right] \qquad (1)$$

where a is the number of particle pairs per unit area divided by the number of particle pairs per unit volume; b is the true area of contact per particle pair divided by the surface area per particle; c is the mean co-ordination number; H is the interparticle force per unit area whose magnitude is dependent on the interparticle separation, t; t_o is the range of the attractive interparticle force; P_f is the packing fraction of the powder bed i.e. (bed density)/(particle density) and P_{f_0} is the value of P_f when T equals zero. $\bar{d}$, $\bar{s}$ and $\bar{v}$ are the mean effective particle diameter, surface area and volume, respectively.

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To overcome the difficulty of deducing the values of P_{f_0} and t_o when T = 0 and t is large, Chan et al (1983) introduced the concepts of a reference state and a reduced tensile strength, R:

$$R = \frac{T}{\frac{\bar{d}\,\bar{s}}{4\bar{v}}\,\frac{P_f}{1 - P_f}} \qquad (2)$$

and

$$R = \frac{\alpha}{t^m} \qquad (3)$$

where

$$\alpha = \frac{k\,z\varepsilon_o}{t_o^{(3-m)}} \qquad (4)$$

α is a parameter characteristic of each material (Chan et al 1983; Bangudu & Pilpel 1984), m is a universal constant whose value is approximately unity, k is a constant relating the co-ordination number to P_f, ε_o is an energy parameter and z is a universal constant used in the enumeration of the area of contact between particles.

Materials and methods

The materials used were metronidazole BP, lactose BP and maize starch BP and the following binding agents: polyvinylpyrrolidone, PVP, mol. wt 44 000, gelatin IP and methylcellulose 20 BPC as described previously (Itiola & Pilpel 1986a,b).

Preparation and characterization of powders. Batches (250 g) of a basic formulation of metronidazole (56% w/w), lactose (32% w/w) and maize starch (12% w/w) were granulated either with distilled water or with various amounts of solutions or mucilages of the different binding agents as described previously (Itiola & Pilpel 1986a,b). The granules, as well as the individual ingredients metronidazole, lactose and maize starch, were milled down to fine powder in a laboratory universal mill C100 LU (Alpine, Augsburg) and fractionated using a Microplex zig-zag classifier (Alpine, Augsburg, FRG) in order to obtain the size range of <25 μm for all the samples. The degree of mixing of these <25 μm powders was determined by chemical assay of metronidazole (British Pharmacopoeia 1980) and was found to be >0·96. The particle densities, ρ_s, of the samples were determined using the Beckman air comparison pycnometer (Model 930, Beckman Instruments). Their particle size distributions were deter-

mined by optical microscopy on about 600 particles from each sample and were used to calculate the values of $\bar{d}$, $\bar{s}$ and $\bar{v}$ of the samples (Itiola 1986). The values of these parameters for the individual ingredients are given in Table 1.

Table 1. Particle size parameters.

Ingredient	$\bar{d}$ μm	$\bar{s}$ $(\mu m)^2$	$\bar{v}$ $(\mu m)^3$	ρ $g\,cm^{-3}$
Metronidazole	5·7	25·7	469·4	1·443
Lactose	7·0	38·1	999·3	1·545
Maize starch	10·0	76·5	1025·4	1·479

Tensile tests. The tensile strengths of the powders were measured at 40 ± 5% r.h. and 20 ± 1 °C with a tensile tester whose design and operation have been described elsewhere (Ashton et al 1964).

Preparation and evaluation of tablets. The samples' ratios of elastic recovery to plastic compression (ER/PC) were determined while forming them into 10·5 mm diameter flat faced tablets of 500 mg with a packing fraction of 0·90 in a Dartec universal testing machine (Dartec Ltd). The machine can operate at speeds between 0 and 10 cm s^{-1}. The strain rate used was 0·05 cm s^{-1}. The samples' brittle fracture index values (BFI) were also determined by comparing the tensile strengths of tablets made on a hand press (Research and Industrial Instruments, London) with and without a hole at their centre (Hiestand et al 1977) as described previously (Itiola & Pilpel 1986a).

Results and discussion

Fig. 1 shows a linear relationship between log R and log t for representative samples obtained by using the trial and error method of Chan et al (1983). The slopes of these lines give −m, a universal constant with a value of 1·00 ± 0·14, and their intercepts at log t = 0. i.e. t = 1 μm give the material constant α. The values of α for all the samples are given in Table 2 and are seen to vary from 0·61 to 4·18 (kNm^{-2} μm). α is a measure of the intrinsic interactions between the particles of the

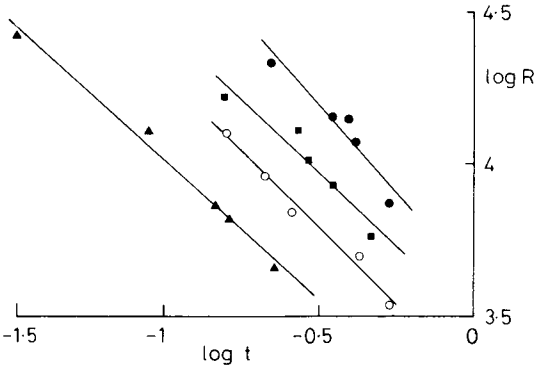

FIG. 1. Plot of log R versus log t for representative samples. ●, metronidazole; and formulations containing different concentrations of PVP ○ = 1%, ■ = 3%, ▲ 10% w/w.

Table 2. Values of α, ER/PC and BFI for metronidazole formulations and excipients.

Binder and other components	Concn of binder (% w/w)	α (kNm^{-2} μm)	ER/PC	BFI
	0·00	2·44	4·55	0·423
PVP	1·00	1·92	3·90	0·408
	2·00	3·42	3·54	0·389
	3·00	3·07	3·23	0·379
	5·00	2·27	3·00	0·357
	7·50	2·08	2·83	0·318
	10·00	1·24	2·70	0·252
Gelatin	0·25	1·79	3·85	0·410
	0·50	1·55	3·57	0·404
	1·00	1·98	3·32	0·389
	2·00	2·57	3·14	0·375
	3·00	2·55	2·97	0·324
	5·00	1·79	2·80	0·275
Methylcellulose	0·50	3·03	3·70	0·408
	1·00	2·01	3·45	0·371
	2·00	1·70	3·25	0·339
	2·50	1·50	3·06	0·324
	3·00	1·53	2·83	0·298
Metronidazole		4·18	6·06	*
Lactose		1·65	4·47	0·246
Maize starch		0·61	9·88	0·336

* Not measurable due to capping.

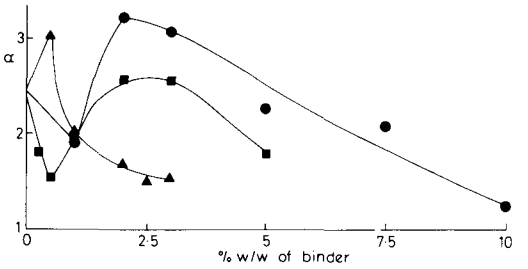

FIG. 2. Plot of α (kNm^{-2} μm) versus % w/w of binder in the formulation. ● PVP, ■ gelatin, ▲ methylcellulose; metronidazole is on the ordinate at α = 4·2.

samples and has the dimension of work. Hence low α values imply relative ease of compression. Metronidazole on its own has a much higher value of α than the formulations. It is difficult to compress and its tablets laminate or cap. Fig. 2 shows that the values of α for the formulations depend on the nature and concentration of binder used.

The basic formulation of the drug has a much lower α value than metronidazole because of the presence of two excipients—lactose and maize starch—with low values of α which reduce the interactions between the particles of the drug. On the incorporation of the soft binding agents which have low interactions between their particles (Kurup & Pilpel 1979), there is an initial complicated variable behaviour with minima and/or maxima in the values of α probably due to changes in the level of the various interactions between the drug, excipients and binder as the binder concentration is increased. At higher concentrations of the binders, their properties predominate and the values of α exhibit a progressive decrease.

The values of ER/PC and BFI for all the samples are included in Table 2. The ER/PC values vary from 2·70 to 9·88 while the BFI values vary from 0·246 to 0·423. Fig. 3 shows how the values of ER/PC and BFI of the formulations vary with the nature and concentration of binder present. In a previous investigation (Itiola & Pilpel 1986a), we showed that the ER/PC values provide an inverse measure of the bond strength of the tablets while the BFI values provide a measure of the tendency of the tablets to laminate or cap.

Obviously, α should have some influence on the tableting properties of the formulations. A reduction in the value of α should facilitate compression. In agreement with this, tablets made from the formulations do not exhibit fracture problems as severe as those of metronidazole. However, fracture problems remain especially when the BFI of the formulation is >0·370. This suggests that the influence of α on the tableting properties of the formulation is limited. This is supported by a comparison of the plots in Figs 2 and 3. The variations of α of the formulations with binder concentration (Fig. 2) do not generally correlate with the bond strengths of the tablets (Fig. 3) nor with the tendency of

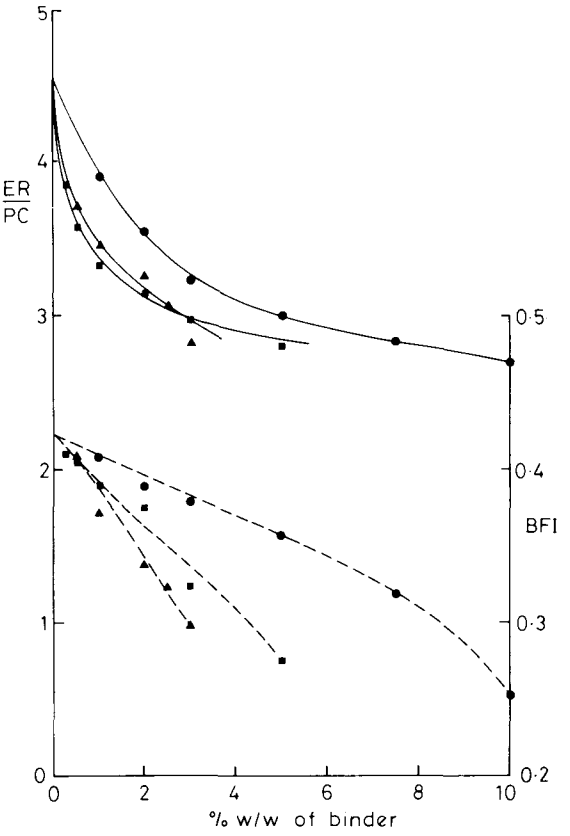

FIG. 3. Plot of % w/w of binder versus the values of ER/PC (——) and BFI (— — —) for the formulations. ● PVP, ■ gelatin, ▲ methylcellulose.

the tablets to laminate or cap (Fig. 3). Under the high compressional forces employed for tableting, the binding agents deform plastically and are forced into the interparticle spaces where they increase the area of contact between particles and form strong solid bonds. The large plastic compression results in low ER/PC values (Itiola & Pilpel 1986a) which have a greater effect on the tableting properties of the formulations than α.

However, it appears that α becomes more influential as ER/PC increases. This is supported by a consideration of two of the individual ingredients—metronidazole and maize starch with relatively high ER/PC values. The BFI of metronidazole could not be measured, but the fact that its tablets cap or laminate can be explained by the combination of its high α and high ER/PC values. On the other hand, though maize starch has a high ER/PC value, it also has a particularly low α value and this probably accounts for the fact that maize starch forms satisfactory tablets on its own.

It seems probable that α could supplement the information obtained from indices such as ER/PC and BFI on the tableting characteristics of pharmaceutical materials.

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Determination of the apparent failure viscosity of tablets

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Quantitative differences in the plasticity of several direct compression excipients were found to be distinguishable using normalized work of failure determinations. New parameters were developed to characterize the importance of changes in strain rate application during a diametral crushing test. Failure viscosity was found to have a similar sensitivity to normalized work of failure measurements and was also able to distinguish small changes in plastic behaviour. In cases where it is not possible to measure tablet deformation during tablet crushing, failure viscosity determinations could provide an alternative method for characterizing differences in deformation behaviour.

The tension test was first used for testing pharmaceutical tablets by Newton & Fell (1968), when a tablet was placed along its edge between two flat platens. The deformation undergone by the tablet during diametral testing has been measured by Rees & Rue (1978). The measured deformation of the tablet is not a true tensile strain, but a deformation of the tablet in the direction of compressive loading. Those workers calculated the area under the force applied versus tablet deformation curve and related this parameter to the toughness of the tablet as defined by Dieter (1961). Rees & Rue (1978) termed the calculated area 'work of failure' (WF) which was calculated according to equation 1.

$$WF = \int_0^x F.\,dx \qquad (1)$$

where F is the force applied and x is the tablet deformation.

However WF does not take into account the rate of crack propagation through the tablet prior to failure. It has been recently reported (Patel et al 1987) that the rate of fatigue crack propagation is influenced by the physicomechanical properties of the powder; the latter also governs the degree of interparticle bonding during compaction. One possible parameter that can be derived is the 'power of failure' i.e. the total power expended in causing tensile failure of the tablet, which can be calculated by dividing the work performed to cause tensile failure (WF) by the time of load application. By treating tablets as non-Newtonian plastic solids, another parameter can be derived, 'apparent failure viscosity' (AFV) with units of stress per strain rate (Pas).

Materials and methods

Materials. Anhydrous lactose (Sheffield Chem. Co., USA), Tablettose (Meggle Milchindustrie, GmbH, Reitmehring, FRG), Dipac (Amstar Corp., NY, USA), Nutab (Ingredient Tech. Corp., NJ, USA), Emcompress (Edward Mendell Co., Carmel, USA) and magnesium stearate (BDH Chemicals, Poole, UK) were used.

Methods. Powders to be compressed were stored for 48 h at 25 °C, 55% r.h. before mixing with 1% w/w magnesium stearate and compressed at a compaction rate of 75 tablets min^{-1} to produce tablets each weighing 500 mg. Compressional work was carried out on a single station reciprocating tableting machine (Manesty, type E2, Manesty Ltd, Speke, Liverpool, UK) fitted with strain gauge-instrumented 12·7 mm flat-faced punches. The complete system for tablet compression, including analogue–digital conversion data acquisition and manipulation to determine the force applied during compaction has been fully described elsewhere (Patel 1986). The compressed tablets were stored for 48 h at 25 °C, 55% r.h. before mechanical testing. A tensile tester (type T22K, JJ Lloyd Instr., Southampton, UK) was used for determinations of the tensile strength, NWF values.

$$NWF = \frac{2\pi}{DT} \int_0^x F.\,dx \qquad (2)$$

where NWF is the normalized work of failure, D is the tablet diameter, T is the tablet thickness, F is the force applied and x is the tablet deformation.

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