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Tableting characteristics of metronidazole formulations

O.A. Itiola and N. Pilpel

Chelsea Department of Pharmacy, King's College London, University of London, London SW3 6LX (U.K.)

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Summary

A study has been made of the effects of polyvinylpyrrolidone, gelatin and methylcellulose binding agents on the tableting properties of a metronidazole–lactose–starch formulation and on the tensile strengths (T) of tablets produced from both granular and powdered forms of the formulation. The samples' elastic recovery to plastic compression ratios (ER/PC) and their brittle fracture index values (BFI — obtained by comparing tensile strengths of tablets with and without a hole at their centre) decreased with binder concentration while T increased. Tablets made from granules (TABG) had lower T and higher ER/PC than those from powders (TABP) but were also less brittle. Tablets made from granules (TABG) exhibited no fracture problems during the compression cycle but were friable at low concentrations of binders. On the other hand, tablets made from powders (TABP) were non-friable but occasionally laminated or capped. These observations might be anticipated from the measured values of ER/PC and BFI of the materials.

Introduction

The tableting characteristics of numerous pharmaceutical materials, which depend on their plastic and elastic behaviour during the compression/decompression/ejection cycle, have been widely studied by the use of various techniques (Krycer et al., 1982a). Plastic compression (PC) of materials under constant load has been used as a measure of their plastic deformation and has been defined (Malamataris et al., 1984) as

$$PC = \left[(H_p - H_t)/H_t\right] \times 100\% \qquad (1)$$

where H_p and H_t are the thicknesses of the tablet, respectively, at maximum pressure and after being held for 30 s at maximum pressure. This involves the considerably simplifying assumption that deformation is directly proportional to a change in thickness (Bangudu and Pilpel, 1985). The value of PC will be influenced by a number of experimental variables including the rate of loading, the magnitude of the applied force, the time for which it is held, the dimensions and state of the punches and die used and die wall reaction effects. Similarly, the elastic recovery (ER) of materials during decompression has been defined (Krycer et al., 1982b) as

$$ER = \left[(H_0 - H_p)/H_p\right] \times 100\% \qquad (2)$$

where H_0 is the thickness of the tablet after ejection and 24 h storage. The equation does not allow for the possibility of elastic recovery in a

Correspondence: N. Pilpel, Chelsea, Department of Pharmacy, King's College London, University of London, Manresa Road, London SW3 6LX, U.K.

radial direction after removal from the die but nevertheless it has been used effectively as a comparative measure of the disruptive effects of elastic deformation (Krycer et al., 1982a). Malamataris et al. (1984) and Bangudu and Pilpel (1985) have employed the ratio ER/PC as a comparative measure of plasto-elasticity for assessing the tableting properties of pharmaceutical materials.

On the other hand, Hiestand et al. (1977) have devised a test based on the Griffith fracture theory for obtaining what they have termed the brittle fracture index (BFI). This is obtained by comparing the tensile strengths of tablets with a hole at their centre, which acts as a built-in stress concentrator 'defect', with the tensile strengths of tablets without a hole. The BFI is defined as

$$BFI = \frac{T - T_0}{2T_0} \qquad (3)$$

($0 \leqslant BFI \leqslant 1$) where T is the tensile strength of the tablet without a hole and T_0 is the apparent tensile strength of the tablet when a hole is present – both at the same packing fraction. The BFI is an inverse measure of localized stress relief within the tablet by plastic deformation and is used to indicate the tendency of a tablet to cap or laminate.

Metronidazole, which is widely used for the treatment of trichomonal infections of the genito-urinary tract, intestinal amoebiasis and giardiasis (Anon, 1982), cannot be made into satisfactory tablets on its own due to lamination and capping problems. It is therefore produced commercially in the form of tablets containing between 40% and 60% w/w of the drug with added excipients (Martindale, 1982) which modify its plastic and elastic properties. The tableting properties depend considerably on the nature and quantity of the soft and plasto-elastic binding agents employed in the formulation (Healey et al., 1972; Esezobo and Pilpel, 1976; Kurup and Pilpel, 1977) and also on the physical form of the formulation (Ganderton and Hunter, 1971). Rees and Rue (1978) and Hiestand and Smith (1984) have shown that though the value of a single index such as the BFI (or ER/PC) may provide a useful measure of the properties of the formulation, it is of limited value in assessing the variety of tableting properties that may be exhibited.

In the present work, a study has been made of the effects of the type and amount of binding agent employed in metronidazole formulations in both granular and powdered forms, on their tableting characteristics and on the tensile strengths of the resulting tablets using both ER/PC and BFI as assessment parameters.

Materials and Methods

The materials used were metronidazole BP (May and Baker, Dagenham, Essex), lactose BP (Dairy Crest, Surrey) and maize starch BP (BDH Chemicals, Poole) and the following binding agents: Polyvinylpyrrolidone, PVP, MW 44,000 (BDH Chemicals, Poole), gelatin IP (Chemical and Instruments, Calcutta) and methylcellulose 20 BPC (Thornton and Ross, Huddersfield).

Preparation of granules and powders

250 g batches of mixtures of metronidazole (56% w/w), lactose (32% w/w) and maize starch (12% w/w) were dry-mixed for 5 min in a Kenwood planetary mixer and then moistened either with 40 ml of distilled water or with appropriate amounts of aqueous solutions (PVP or gelatin) or mucilages (methylcellulose) to produce granules containing different concentrations of the different binding agents. Massing was continued for 3 min and the wet masses were granulated by passing them manually through a number 12 mesh sieve, dried in a hot air oven for 18 h at 50°C and then resieved through a number 16 mesh sieve. Their degrees of mixing were determined by chemical assay of metronidazole (BP 1980) and were found to be > 0.955. Some of the granules were milled down into powdered form in a laboratory universal mill C100 LU (Alpine, Augsburg) and fractionated using a Multiplex zig-zag Classifier (Alpine, Augsburg, F.R.G.) The moisture contents of the formulations, as determined with a vacuum moisture tester (Townson and Mercer, Croydon) were between 2.2% and 2.8% w/w. The individual ingredients metronidazole, lactose and maize starch were also milled down and fractionated into different size ranges. Particle densities were determined using the Beckman air comparison pycnometer (Model 930, Beckman Instruments).

Preparation of tablets

To determine the BFI of the formulations and excipients, 500 mg tablets were prepared from the 1000–1400 μm size fraction of granules (TABG) and from the < 25 μm size fraction of powders (TABP) by compressing them for 1 min with predetermined loads using a hand press fitted with a pressure gauge reading up to 5.0 tons (Research and Industrial Instruments, London). Before each compression, the die (10.5 mm diameter) and the flat-faced punches were lubricated with a 1% w/v dispersion of magnesium stearate in chloroform. Tablets with a hole (1.59 mm diameter) at their centre were made by using an upper punch with a hole through the centre and a lower punch fitted with a pin (Fig. 1). After ejection, the tablets were stored over silica gel for 24 h to allow for elastic recovery and hardening. Their weights, W and dimensions were then determined to within ± 1 mg and 0.01 mm and their packing fractions P_f, were calculated using the equation

$$P_f = W/V_t \cdot \rho_s \qquad (4)$$

where V_t is the volume of the tablet (including the hole when present) in cm^{-3} and ρ_s is the particle density of the solid material in $g \cdot cm^{-3}$.

To measure the plasto-elasticity of the samples, 500 mg of each was formed into a conventional tablet in a Dartec 100 KN M2501 universal testing machine (Dartec) connected to a Bryans X–Y recorder using a 10.5 mm diameter die and flat-faced lower and upper punches – the latter connected to a load cell with a sensitivity of ± 1 N. The limit ramp was set to 20% and the load rate to 0.667 $kN \cdot s^{-1}$ resulting in the application of loads up to 20 kN over 30 s. The loads were adjusted to give tablets with a packing fraction of 0.90 which is representative of commercial metronidazole tablets. These were held manually for 30 s, then released automatically over 30 s. The tablet was ejected over a further 30 s by inverting the die and using the upper punch. The whole cycle occupied 2 min. The punches and die were lubricated before each compression and the resulting tablets were stored for 24 h and their weights and dimensions subsequently measured as previously described. The X–Y recorder plotted the load versus the displacement of the upper punch from which the values of PC and ER were calculated using Eqns. 1 and 2, respectively.

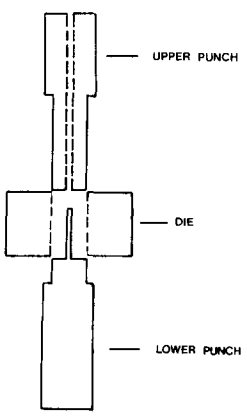

Fig. 1. Schematic diagram of punches and die for making tablets with a central hole.

Testing

The tensile strengths, T, of the normal tablets and T_0, of those containing a hole were measured at room temperature by diametral compression (Fell and Newton, 1970) using a CT40 tester (Engineering systems, Nottingham) and applying the equation

$$T = \frac{2P}{\pi Dt} \qquad (5)$$

where T (or T_0) is the tensile strength of the tablet in $MN \cdot m^{-2}$, P is the load needed in MN to cause fracture, D is the tablet diameter in m and t is the tablet thickness in m. Standard cardboard padding strips (0.45 mm thick and 2.5 mm wide) were positioned at the contact points between the tablets and plates in the CT40 during tests to ensure even distribution of stress (York and Pilpel, 1973). Results were taken only from tablets which split cleanly into two halves without any sign of lamination. All measurements were made in triplicate or more and the results given are the means of several determinations.

The BFI of the tablets were calculated using Eqn. 3. It was not found possible to measure the tensile strength and hence the BFI value of tablets made from metronidazole alone. These tablets

laminated or capped from which it may be inferred that the BFI of metronidazole approaches 1.0 (Hiestand et al., 1977). It was, however, possible to obtain its ER/PC value from the Dartec measurements.

Results and Discussion

Binding agents employed in formulations deform plastically during compression and are forced into the interparticulate spaces where they increase the area of contact between particles and form strong solid bonds (Esezobo and Pilpel, 1977; Kurup and Pilpel, 1979). The number and strength of bonds formed depend on the nature and amount of binder employed. This explains the observed increase in PC and decrease in ER with increase in binder content of the formulations as presented in Table 1. Increasing the binder concentration reduced the value of ER/PC and increased the value of T of the resulting tablets. Tablets made from granules (TABG) had lower T and higher ER/PC values than those made from powders (TABP). This inverse relationship between T and ER/PC is shown in Fig. 2 and has been established for other pharmaceutical materials by Malamataris et al. (1984) and Bangudu and Pilpel (1985). ER/PC is an inverse measure of bond strength since T is determined by the sum of all the bonds in the tablet (Nyström et al., 1982). PC provides a measure of the areas of interparticulate bonding while ER is responsible for the rupture of bonds due to elastic reassertion when the pressure is withdrawn. The net number of bonds remaining after decompression will be expected to depend on the relative magnitudes of PC and ER.

It was found during the determinations of BFI

TABLE 1

PLASTO-ELASTIC PARAMETERS AND TENSILE STRENGTH ($MN \cdot m^{-2}$) OF METRONIDAZOLE TABLETS AND EXCIPIENTS AT $P_f = 0.90$

Binder and other components	Concn. of binding (% w/w)	Tablets made from granules (TABG)				Tablets made from powders (TABP)			
		PC	ER	ER/PC	T ($MN \cdot m^{-2}$)	PC	ER	ER/PC	T ($MN \cdot m^{-2}$)
	0.00	1.67	9.89	5.92	1.170	2.41	10.96	4.55	2.059
PVP	1.00	1.96	8.89	4.54	1.501	2.61	10.18	3.90	2.913
	2.00	2.07	8.52	4.12	1.830	2.73	9.67	3.54	3.349
	3.00	2.15	8.41	3.91	1.911	2.83	9.14	3.23	3.658
	5.00	2.33	8.12	3.49	1.977	3.04	9.11	3.00	3.992
	7.50	2.38	7.82	3.29	2.096	3.10	8.78	2.83	4.095
	10.00	2.48	7.52	3.03	2.272	3.16	8.54	2.70	4.442
Gelatin	0.25	1.89	8.64	4.57	1.261	2.65	10.20	3.85	3.043
	0.50	1.92	8.27	4.31	1.302	2.84	10.13	3.57	3.138
	1.00	2.07	7.79	3.76	1.461	2.87	9.53	3.32	3.194
	2.00	2.10	7.57	3.61	1.510	2.92	9.18	3.14	3.272
	3.00	2.15	7.68	3.57	1.530	2.94	8.72	2.97	3.381
	5.00	2.24	7.52	3.36	1.693	3.04	8.52	2.80	3.588
Methylcellulose	0.50	1.77	8.31	4.70	1.003	2.51	9.28	3.70	2.312
	1.00	2.04	8.06	3.95	1.232	2.59	8.94	3.45	2.595
	2.00	2.09	7.71	3.69	1.460	2.66	8.64	3.25	3.026
	2.50	2.13	7.49	3.52	1.576	2.70	8.26	3.06	3.267
	3.00	2.26	7.39	3.27	1.720	2.89	8.18	2.83	3.578
Metronidazole	–	–	–	–	–	2.07	12.54	6.06	capped
Lactose	–	–	–	–	–	1.91	8.53	4.47	3.068
Maize starch	–	–	–	–	–	1.79	17.69	9.88	1.563

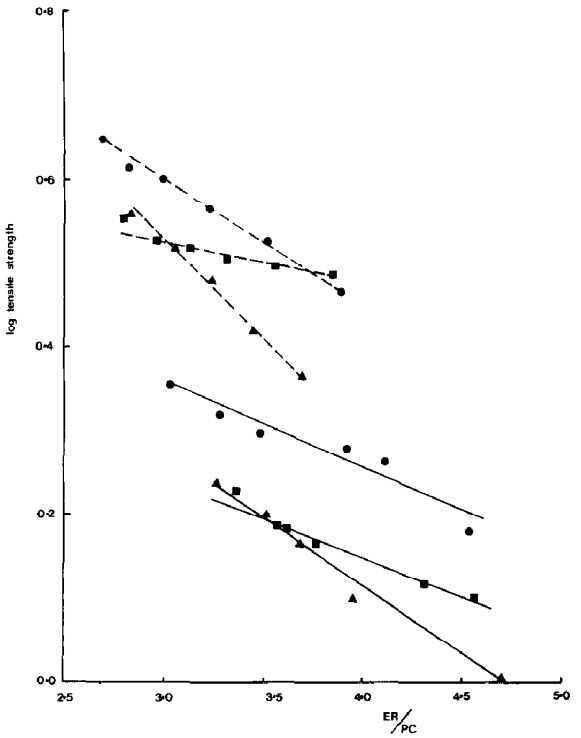

Fig. 2. Log tensile strength versus ER/PC at $P_f = 0.90$ for metronidazole tablets made from granules (TABG; ———) and from powders (TABP; — — —). ●, PVP; ■, gelatin; ▲, methylcellulose.

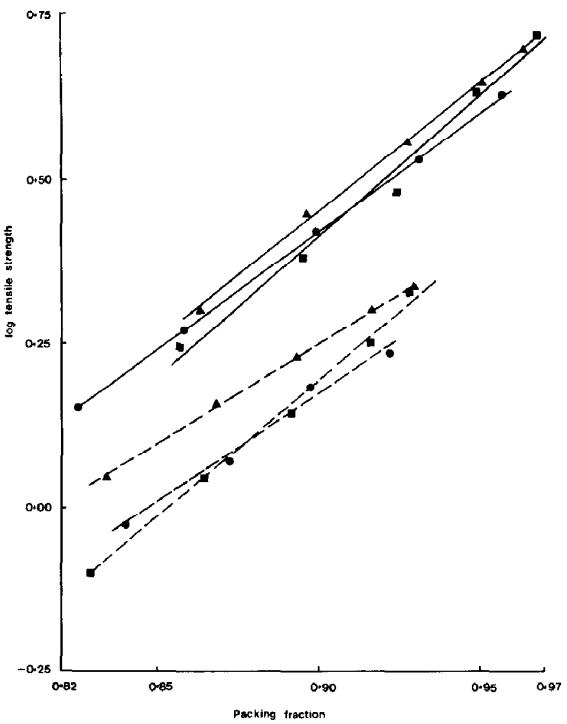

Fig. 3. Log tensile strength versus packing fraction for metronidazole tablets made from powders (TABP) containing 3% w/w of binder without a hole at their centre (———) and with a hole at their centre (— — —). ●, PVP; ■, gelatin; ▲, methylcellulose.

that as expected (York and Pilpel, 1973) there was a logarithmic relationship between T (or T_0) and P_f:

$$\log T \text{ (or } T_0) = AP_f + B \qquad (6)$$

with a correlation coefficient > 0.98. A and B were constants which depended on the nature and amount of binder present in the formulation and on whether the tablet had a hole in it or not. Representative plots for tablets made from powders (TABP) containing 3% w/w of the binders are given in Fig. 3. It is seen that at all packing fractions the tensile strength of a tablet with a hole was less than that of the same without a hole, the hole acting as a stress concentrator (Hiestand et al., 1977). Values of T, T_0 and BFI at P_f of 0.90 for all samples are presented in Table 2. T was always $> T_0$; the values of both increased with binder concentration, the value of BFI decreased. This indicates that the presence of a binder at interparticulate junctions facilitates plastic deformation for the relief of localized stresses. Tablets made from granules (TABG) had lower T values than those made from powders (TABP) but were also less brittle as indicated by their lower BFI values.

The values of ER/PC and BFI for the individual ingredients (Tables 1 and 2) provide some insight into their qualitative effects on the tableting properties of the formulations. ER/PC values for all the powder samples varied from 2.70 to 9.88 while their BFI values varied from 0.246 to 0.423. The low value of BFI for lactose indicates that lactose aids the plastic deformation of the formulations during compression. On the other hand, the high ER/PC value for maize starch implies that maize starch weakens the strengths of the bonds in tablets.

Considering the present results in terms of the

TABLE 2

TENSILE STRENGTH ($MN \cdot m^{-2}$) AND BRITTLE FRACTURE INDEX VALUES OF METRONIDAZOLE TABLETS AND EXCIPIENTS AT $P_f = 0.90$

Binder and other components	Concn. of binder (% w/w)	Tablets made from granules (TABG)			Tablets made from powders (TABP)		
		T ($MN \cdot m^{-2}$)	T_0 ($MN \cdot m^{-2}$)	BFI	T ($MN \cdot m^{-2}$)	T_0 ($MN \cdot m^{-2}$)	BFI
	0.00	0.678	0.485	0.199	1.656	0.897	0.423
PVP	1.00	1.239	0.918	0.175	2.114	1.164	0.408
	2.00	1.641	1.247	0.158	2.535	1.426	0.389
	3.00	1.718	1.334	0.144	2.630	1.496	0.379
	5.00	1.807	1.476	0.112	2.871	1.675	0.357
	7.50	1.866	1.671	0.058	3.083	1.884	0.318
	10.00	1.995	1.845	0.041	3.524	2.344	0.252
Gelatin	0.25	1.062	0.811	0.155	2.254	1.239	0.410
	0.50	1.288	1.002	0.143	2.270	1.256	0.404
	1.00	1.324	1.054	0.128	2.427	1.365	0.389
	2.00	1.419	1.172	0.105	2.512	1.436	0.375
	3.00	1.563	1.306	0.098	2.582	1.567	0.324
	5.00	1.675	1.483	0.065	2.661	1.718	0.275
Methylcellulose	0.50	0.935	0.716	0.153	2.466	1.358	0.408
	1.00	1.191	0.955	0.124	2.570	1.476	0.371
	2.00	1.503	1.253	0.100	2.618	1.560	0.339
	2.50	1.556	1.315	0.092	2.673	1.622	0.324
	3.00	1.644	1.413	0.082	2.825	1.770	0.298
Metronidazole	–	–	–	–	capped	capped	–
Lactose	–	–	–	–	3.027	2.028	0.246
Maize starch	–	–	–	–	1.189	0.711	0.336

tableting performance of the different formulations, the granules generally produced satisfactorily strong tablets which did not cap or laminate and only became friable when the concentration of binder was low (< 1% w/w). On the other hand, tablets made from powders (TABP), despite their higher T and lower ER/PC values, sometimes laminated or capped during decompression and/or ejection from the die especially when their BFI value was > 0.370. When this occurred the individual pieces were quite strong indicating extensive localized plastic deformation during compression; hence fracture was probably due to the presence of weak points within the tablet. Interparticulate friction between the particles of the cohesive powder samples contributes to variations in the degree of packing of the powders in the die. There can be quite large local variations in the density of the tablet and in the amount of plastic compression that has occurred (Train, 1956; Carstensen, 1980) with fracture probably emanating from the regions of lowest density during decompression and ejection. On the other hand, granules are known to fragment during compression and fill up void spaces between particles (Shotton and Ganderton, 1960; Esezobo and Pilpel, 1977), thus minimizing local density variations in the resulting tablets.

It appears that ER/PC and BFI measure essentially different properties of tablets. ER/PC seems to be more related to bond strength, the BFI appears to be a measure of the tendency of a tablet to fracture. It may be concluded that in formulation studies the combined use of the two indices can provide useful information on the tableting characteristics of pharmaceutical materials. The absolute values of the indices will, however, be expected to vary with the detail of the test conditions employed.

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