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Formulation Effects on the Mechanical Properties of Metronidazole Tablets

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Abstract—The individual and interaction effects of nature of binder (N), concentration of binder (C) and the physical form of the formulation (P) on the tensile strengths (T—a measure of the bond strength of tablets) and the brittle fracture index values (BFI—a measure of the lamination tendency of tablets) of metronidazole tablets have been studied using a 2^3 factorial experimental design in each case. Changing binder concentration from a 'low' to a 'high' level increased T and reduced the BFI of the tablets. Methylcellulose 20 exhibited stronger binding effect and greater ability to reduce the lamination tendency of the tablets than polyvinylpyrrolidone of molecular weight 44 000. Granular formulations produced tablets with lower T values but also with lower BFI values than tablets produced from powdered formulations. The ranking of these individual effects on tensile strength was P > C > N while the ranking for the BFI was P > N > C. For the interaction effects, the ranking for tensile strength was P—N ≫ N—C > P—C while the ranking for the BFI was N—C ≫ P—C > P—N.

Recently, Itiola & Pilpel (1986a) studied the mechanical properties of metronidazole tablets and differentiated between the bond strength of the tablets as measured by their tensile strengths and the tendency of the tablets to laminate or cap as measured by their brittle fracture index values.

The brittle fracture index (BFI) was devized by Hiestand et al (1977). It 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

$$\mathrm{BFI} = 0{\cdot}5\left[\frac{T}{T_o} - 1\right] \qquad (1)$$

where T is the tensile strength of the tablet without a hole and T_o is the apparent tensile strength of the tablet when a hole is present—both at the same packing fraction. The BFI is a measure of localized stress relief within the tablet (at the edge of the hole) by plastic deformation. A low value of the BFI indicates the ability of the material to relieve localized stresses while a value approaching unity indicates a tendency of the material to laminate or cap.

With the realization that more than one parameter is required to characterize the mechanical properties of tablets (Hiestand et al 1977; Itiola & Pilpel 1986a, 1987), there is the need to make comparative studies on how formulation factors affect individual parameters.

In the present work, a study has been made of the relative quantitative effects of the nature and concentration of binding agent employed and the physical form of the formulation on the tensile strengths and the brittle fracture index values of metronidazole tablets.

Materials and Methods

Materials

The materials used were metronidazole BP (Rhône Poulenc Ltd, Dagenham, UK), lactose BP (Dairy Crest, Surrey, UK), maize starch BP (BDH Chemicals, Poole, UK), polyvinylpyrrolidone (PVP, mol. wt 44 000, BDH Chemicals, Poole, UK) and methylcellulose 20 BPC (Thornton and Ross, Huddersfield, UK).

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Preparation of granules and 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 with appropriate amounts of PVP solutions or methylcellulose mucilages to produce granules containing either 1 or 3% (w/w) of the binding agents as described previously (Itiola & Pilpel 1986a, b). Some of the granules were milled down into powdered form in a laboratory universal mill C100 LU (Alpine, Augsburg, Germany) and fractionated into different size ranges using a Microplex zig-zag classifier (Alpine, Augsburg, Germany). The degree of mixing of the granules and powders was determined by chemical assay of metronidazole (BP 1980) and was found to be > 0·96. The moisture content of the formulations as determined with a vacuum moisture tester (Townson and Mercer, Croydon, UK) was between 2·6 and 2·7% (w/w). Particle densities were determined using the Beckman air comparison pycnometer (Model 930, Beckman Instruments, Fullerton, CA, USA).

Preparation of tablets

Tablets (500 mg) were prepared from the 1000–1400 μm size fraction of granules and from the < 25 μm size fraction of powders by compressing them for 1 min with predetermined loads using a hydraulic hand press fitted with a pressure gauge reading up to 5·0 tons (Research and Industrial Instruments, London, UK). Before each compression, the die (10·5 mm diam.) and the flat-faced punches were lubricated with a 1% (w/w) dispersion of magnesium stearate in chloroform. Tablets with a hole (1·59 mm diam.) at their centre were made by using an upper punch with a hole through the centre and a lower punch fitted with a pin (Itiola

& Pilpel 1986a). 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

$$P_f = \frac{W}{V_t \cdot \rho_s} \quad (2)$$

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 cm^{-3}.

Testing

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

$$T = \frac{2P}{\pi Dt} \quad (3)$$

where T (or T_o) is the tensile strength of the tablet in MN 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. 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 equation 1.

Experimental design

To study the effects of the formulation factors on T and BFI values of the tablets, each of the three variables—nature of binder (N), concentration of binder (C) and the physical form of the formulation (P)—was employed at a 'high' level (denoted by the subscript H) and a 'low' level (subscript L) in a 2^3 (=8) factorial experimental design (Woolfall 1964). Using the above nomenclature, the eight combinations between the variables were $P_LN_LC_L$, $P_LN_LC_H$, $P_LN_HC_L$, $P_LN_HC_H$, $P_HN_LC_L$, $P_HN_HC_L$, $P_HN_LC_H$ and $P_HN_HC_H$, where

P_L = powdered formulation, P_H = granular formulation, N_L = nature of binder (PVP), N_H = nature of binder (methylcellulose), C_L = low concentration of binder (1% w/w), C_H = high concentration of binder (3% w/w).

The combinations were grouped into appropriate sets which made it possible to assess the effect that each variable had separately on the mechanical properties of the tablets and also to determine whether the variables were interacting or acting independently of each other. For example, the effect of increasing P from its 'low' level to its 'high' level on tensile strength was found by summing all tensile strength results from samples containing 'high' levels of P and subtracting the sum of the tensile strength results from the samples containing 'low' levels of P.

The amount by which the result of this treatment departed from zero (irrespective of whether positive or negative) was a quantitative measure of the effect of P on the tensile strength of the tablets. Similar expressions were used for finding the effects of N and C. The process was repeated using the BFI results.

To determine whether there was any interaction between two variables the T (or BFI) results of the combinations in which they appeared together at either 'high' or 'low' levels were summed and the sum of the other combinations subtracted from this. A result of zero indicated no interaction, but a significant departure from zero implied that the two variables were interacting with each other.

Similar expressions were used for estimating the interactions between P and C and between N and C.

Results and Discussion

The results of the tensile tests on the tablets were found to fit the general equation:

$$\log T \text{ (or } T_o) = AP_f + B \quad (4)$$

with a correlation coefficient >0·985. A and B were constants which depended on the variables' combination present and on whether the tablet had a hole in it or not. Fig. 1 shows representative plots for tablets made from combinations $P_LN_LC_H$ and $P_LN_HC_H$. It is seen that at all packing fractions the tensile strength of a tablet with a hole was lower than that of the same without a hole, the hole acting as a stress concentrator (Hiestand et al 1977). Values of T and BFI for all combinations at P_f of 0·90 which is representative of commercial metronidazole tablets are presented in Table 1. These values were used to calculate the independent and interaction coefficients for the variables using the relevant expressions. The values are presented in Table 2. There were both positive and negative influences on the mechanical properties of the tablets. A positive influence indicates that the T (or BFI) value has increased while a negative influence indicates that the value of the parameter has decreased. Obviously, a negative effect on the BFI is desirable for the minimization or avoidance of the problem of lamination and capping during tablet production. On the other hand, the

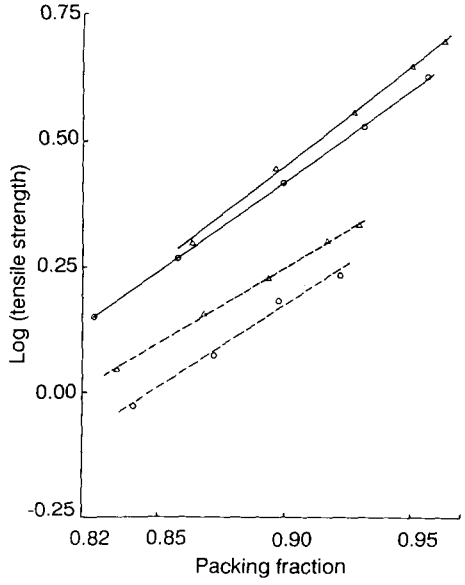

FIG. 1. Log tensile strength vs packing fraction for metronidazole tablets made without a hole at their centre (——) and with a hole at their centre (- - - -). ○, $P_LN_LC_H$; △, $P_LN_HC_H$.

Table 1. Tensile strength and brittle fracture index (BFI) values of metronidazole tablets at $P_f = 0.90$.

Combination of variables	Tensile strength (MN m^{-2})	BFI
$P_LN_LC_L$	2·114	0·408
$P_LN_LC_H$	2·630	0·379
$P_LN_HC_L$	2·570	0·371
$P_LN_HC_H$	2·825	0·298
$P_HN_LC_L$	1·239	0·175
$P_HN_LC_H$	1·718	0·144
$P_HN_HC_L$	1·191	0·124
$P_HN_HC_H$	1·644	0·082

Table 2. Quantitative effects of nature of binder (N), concentration of binder (C) and physical form of formulation (P) on tensile strength and brittle fracture index (BFI) values of metronidazole tablets.

		Independent coefficient	
A.	Variable	Tensile strength (MN m^{-2})	BFI
	P	−1·087	−0·233
	N	0·132	−0·058
	C	0·426	−0·044

		Interaction coefficient	
B.	Variables' combination	Tensile strength (MN m^{-2})	BFI
	P—N	−0·193	0·001
	P—C	0·040	0·007
	N—C	−0·072	−0·014

desirable effect on T depends largely on the intended use of the tablets.

The independent coefficient values (Table 2A) show the individual effects of the variables on the values of T and BFI of the tablets. Differences between the parameters in terms of their dimensions (the BFI is dimensionless) and their absolute values preclude a direct comparison of their coefficient values, but the ranking of the effects can be compared. The ranking for tensile strength was P > C > N. For the BFI, the ranking was P > N > C. The variables' effects on the BFI were all negative. On the other hand, while P had a negative effect on tensile strength, both C and N had positive effects.

The influence of N on tensile strength indicates that methylcellulose 20 which represented the 'high' level of N is a slightly stronger binder than PVP (mol. wt 44 000), while the influence of N on BFI implies that the methylcellulose also has a greater ability to reduce the lamination tendency of the tablets.

The effect of C on tensile strength is well known and the results show that increasing the concentration of the plastoelastic binder used from 1 to 3% (w/w) led to an increase in the plastic deformation of the formulation during compression and subsequently to the formation of more solid bonds in the resulting tablets (Itiola & Pilpel 1986a). The effect of C on the BFI, on the other hand, implies that increasing the binder concentration did not reduce the lamination tendency of the tablets considerably. Hence it would appear that the effect of binder concentration is mainly on the bond strength of the tablets.

P had the largest effects on both T and BFI. The granules produced softer tablets than the powders but also reduced the lamination tendency of the tablets considerably. The effect of P on tensile strength indicates that the granules exhibited lower plastic deformation than the fine powders. On the other hand, the effect of P on BFI can be attributed to the fact that fragmentation of granules during compression results in the filling of void spaces between particles and consequently in the minimization of local density variations in tablets (Itiola & Pilpel 1986a). This serves to reduce the tendency for stress to concentrate in some regions within the tablet.

The interaction coefficient values (Table 2B) indicate the effects of the variables in combination. The ranking of the effects on tensile strength was P—N ≫ N—C > P—C. For the BFI, the ranking was N—C ≫ P—C > P—N. Hence, P—N having the largest interaction effect on tensile strength suggests that C had the most independent influence on T. On the other hand, N—C having the largest interaction effect on BFI implies that the effect of P on BFI was largely independent of the effects of the other two variables. In the light of this, the fact that P exhibited the largest individual effect on BFI could explain why granulation is widely employed for the production of tablets in the pharmaceutical industry.

The results of the present work provide some insight into the effects of the formulation factors used as variables on the bond strength and brittleness of tablets. The individual effects show the relative magnitudes of the effects of the variables on the individual parameters. The interaction effects are also important and the results suggest that formulation factors which exhibit relative independence in their effects could be useful in dealing with particular mechanical problems in tablets.

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