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Studies on metronidazole tablet formulations

O. A. ITIOLA AND N. PILPEL*

Chelsea Department of Pharmacy, King's College, University of London, Chelsea Campus, Manresa Road, London SW3 6LX, UK

Incorporating polyvinylpyrrolidone, gelatin and methylcellulose binding agents in a metronidazole formulation alters the tensile strength, disintegration and dissolution times of the tablets by reducing their wettability as measured by the adhesion tension of water. Correlations have been established between the disintegration times, D and the dissolution times t_{50}, t_{90} and t_1 (derived from the equation of Noyes & Whitney). A correlation has also been established between the adhesion tension of water on the tablets and the disintegration and dissolution times. These correlations depend on the nature and concentration of binder used.

Metronidazole in the form of tablets containing between 40 and 60% w/w of the drug is widely used for the treatment of trichomonal infections of the genito-urinary tract, intestinal amoebiasis and giardiasis (Anon. 1982; Martindale 1982). However in some cases the treatment has been reported to be ineffective and this seems to have been due to low blood levels of the drug in patients (Kane et al 1961; McFadzean et al 1969; McGilveray et al 1978). The bioavailability of the drug depends considerably on the rates of disintegration and dissolution of the tablets (Middleton et al 1964; Wood 1967). These properties in turn depend on the nature and quantity of the binding agents used in the formulation (Healey et al 1972; Esezobo & Pilpel 1976; Kurup & Pilpel 1977).

The wettability of the formulation plays a vital role in the processes of disintegration and dissolution which lead to release of the drug into the blood stream. The wetting and subsequent penetration of liquid into the capillary structure of the tablets are controlled, respectively, by the contact angle of the liquid on the solid surface, θ and by its surface tension, γ (Jones 1981; Igwilo & Pilpel 1983). Fell & Efentakis (1978) have suggested that the product $\gamma \cos \theta$, which they defined as the adhesion tension, could be useful in providing information about the wetting and disintegration characteristics of tablet formulations.

In the present work, a study has been made of the way in which the tensile strength, disintegration and dissolution of metronidazole tablets were affected by the type and amount of binding agent used in the formulation. It was considered of interest to see whether there might be a relation between the disintegration/dissolution characteristics of the tablets and the adhesion tension of water on the formulated solid.

* Correspondence.

MATERIALS AND METHODS

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

Preparation of granules

Batches (250 g) 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 (Rose 1959) were determined by chemical assay of metronidazole (BP 1980) and were found to be >0·955. Particle densities were determined using the Beckman air comparison pycnometer (Model 930, Beckman Instruments).

Preparation of tablets

Tablets of 400 mg were prepared from the 1000–1400 μm size fraction of granules by compress-

ing them for 1 min with predetermined loads at a rate of 0·22 mm s^{-1} 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. After ejection, the tablets were stored over silica gel for 24 h to allow for hardening and elastic recovery. Their weights and dimensions were then accurately measured and their packing fractions calculated (Kurup & Pilpel 1977).

Tensile strength test

The tensile strengths, T, of the tablets were measured at room temperature (20 °C) by diametral compression (Fell & Newton 1970) using a CT40 tester (Engineering systems, Nottingham) using the same equation for the calculation as in previous papers (Esezobo & Pilpel 1976; Adeyemi & Pilpel 1984).

Disintegration and dissolution tests

The disintegration times, D, of the tablets were measured in distilled water at 37 ± 0·5 °C using a BP Manesty disintegration tester.

Their dissolution rates were determined at the same temperature in 1 litre of 0·1 M HCl in a round-bottomed flask, using a paddle positioned 10 cm below the surface of the liquid and a stirring speed of 100 rev min^{-1} (USP XX). The amount of metronidazole that had dissolved after a certain period was determined spectrophotometrically at 277 nm using a CE292 digital UV spectrophotometer (Cecil Instruments, Cambridge) replacing the sample by an equal volume of 0·1 M HCl at the same temperature in order to keep the volume of the dissolution medium constant during the course of the test. All measurements were made in triplicate or more and the results given are the means of several determinations.

Determination of contact angles and adhesion tensions

The contact angles of water (saturated with the basic formulation containing no binder) on the tablets were determined as described by Kossen & Heertjes (1965) and Lerk et al (1976) calculating the values from the following equation:

$$\cos\theta = 1 - \left(\frac{Bh^2}{3(1-\varepsilon)(1-Bh^2/2)}\right)^{\frac{1}{2}} \qquad (1)$$

(for $0 < \theta < 90°$), where h is the height of the liquid drop in cm, ε is the volume porosity of the tablet and B is $pg/2\gamma$, where p is the liquid density in g cm^{-3}, g is 981 cm s^{-2} and γ is the surface tension of the liquid in mN m^{-1}, which was measured with a torsion balance (White Electrical Inst. Co. Ltd, Worcestershire). To ensure that the reproducibility of the contact angles was within ±2%, the drops were delivered from an Agla syringe positioned 0·8 cm above the surface of the tablet and the test assembly was covered with a perspex lid. Measurements were made in quintuplicate on individual tablets. A travelling microscope (Graticules Ltd, Tonbridge) fitted with an X–Y display unit to obtain rapid and reproducible measurements was used to measure h. It was established in preliminary experiments that the absence of any binding agent in the solution used did not cause any disruption of the tablet surface in the short period of measurement. The adhesion tensions, AT, were calculated from the cosine of the contact angles using the equation:

$$AT = \gamma\cos\theta \qquad (2)$$

RESULTS

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

$$\log T = AP_f + B \qquad (3)$$

with a correlation coefficient of >0·995. P_f was the packing fraction, A and B were constants which depended on the nature and amount of binder present. Values of D were plotted as a function of packing fraction. Representative plots for tablets containing 3% w/w of the binders are given in Fig. 1.

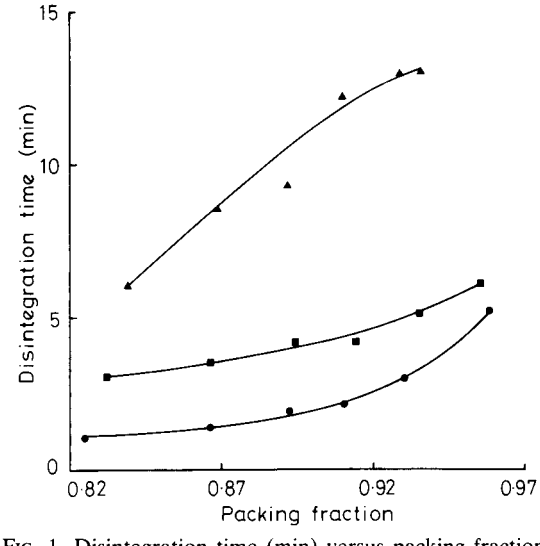

FIG. 1. Disintegration time (min) versus packing fraction (P_f) for metronidazole tablets containing 3% w/w of binder. ●, PVP; ■, gelatin; ▲, methylcellulose.

Typical dissolution profiles for tablets containing 2% w/w of PVP compressed to different packing fractions are shown in Fig. 2. From these, the values

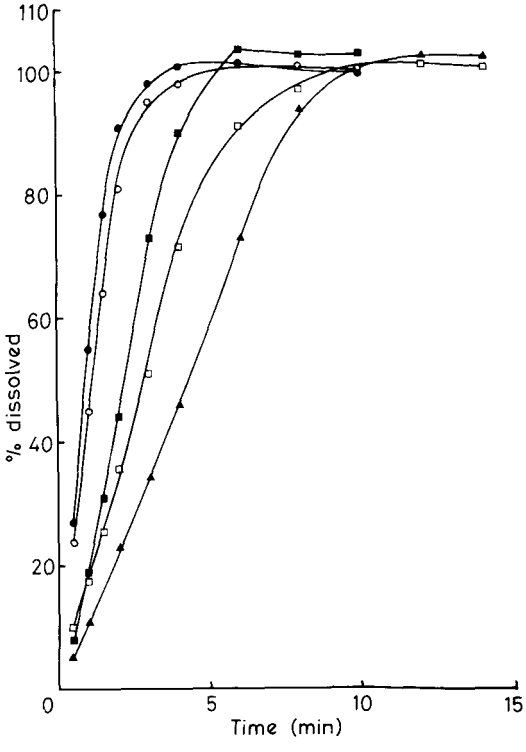

FIG. 2. Effect of packing fraction on the dissolution profiles of metronidazole tablets containing 2% w/w of PVP. Mean P_f: ●, 0·827; ○, 0·857; ■, 0·903; □, 0·930; ▲, 0·947.

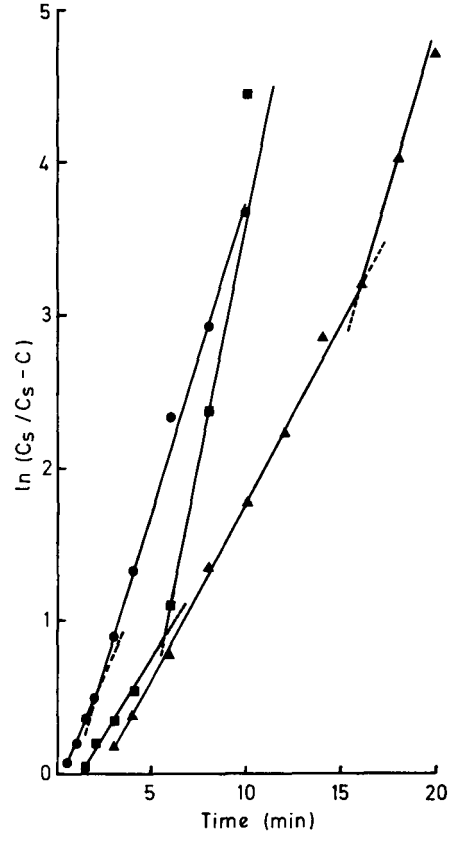

FIG. 3. ln $[C_s/(C_s - C)]$ versus time plots to determine dissolution rate constants for metronidazole tablets containing 3% w/w of binder. ●, PVP, P_f = 0·902; ■, gelatin, P_f = 0·901; ▲, methylcellulose, P_f = 0·914.

of t_{50} and t_{90} (the time required for 50% and 90% of the metronidazole to be released) were calculated.

The integrated form of the equation of Noyes & Whitney (1897) is:

$$\ln [C_s/(C_s - C)] = kt \qquad (4)$$

where C_s is the concentration of the solute at saturation, C is its concentration at time t, and k is a dissolution rate constant. Values of ln $[C_s/(C_s - C)]$ were plotted versus t (Kitazawa et al 1975) as shown typically in Fig. 3. In all cases, except for tablets containing 1% w/w of methylcellulose at certain packing fractions, two straight regression lines of slopes k_1 and k_2 were obtained. The time at which the lines intersect is denoted t_1.

Values of T, D, t_{50}, t_{90}, t_1, k_1 and k_2 for all samples at a selected P_f of 0·90 which is representative of commercial metronidazole tablets are presented in Table 1. It is seen that the values of D, t_{50} and t_{90} all increased with binder concentration. The values of the cosine of contact angle (cos θ) and AT of water on the tablets are presented in Table 2. It is seen that these values decreased with binder concentration. Fig. 4 shows the linear relationships between t_{90} and D and between t_{90} and AT. Table 3 gives the equations of the best fitting straight lines and the correlation coefficients, r, between various measured parameters. These correlations were proved to be significant (P = 0·05) by the construction of standard ANOVA tables, but there was no particular correlation which was significantly better than the others. The correlations between other parameters were found to be poor, e.g. between AT and T (r = −0·744 to −0·892), between AT and k_1 (r = 0·717–0·906) and between AT and k_2 (r = 0·646–0·719).

DISCUSSION

Disintegration of tablets plays a vital role in the dissolution process since it determines the area of

Table 1. Tensile strength, disintegration time and dissolution characteristics of metronidazole tablets at $P_f = 0{\cdot}90$.

Binder	Concn of binder (% w/w)	T ($MN\,m^{-2}$)	D (min)	t_{50} (min)	t_{90} (min)	t_1 (min)	k_1	k_2
	0·00	0·885	0·35	0·50	1·10	1·40	1·800	1·470
PVP	1·00	1·365	0·80	1·30	2·70	2·20	0·570	1·390
	2·00	1·607	1·60	2·10	3·90	1·85	0·305	0·760
	3·00	1·862	2·10	2·20	4·45	2·50	0·290	0·510
	5·00	2·032	4·65	3·40	7·25	4·75	0·175	0·340
	7·50	2·410	6·25	4·80	9·60	8·10	0·165	0·390
	10·00	2·366	10·45	6·45	12·15	9·40	0·130	0·285
Gelatin	0·25	1·746	0·70	1·05	1·65	1·10	0·685	1·760
	0·50	2·138	0·85	1·20	2·35	2·30	0·755	1·190
	1·00	2·188	1·30	1·90	3·75	2·15	0·395	1·060
	2·00	2·018	2·35	2·75	4·45	2·60	0·330	0·710
	3·00	2·128	4·10	4·15	6·90	5·75	0·195	0·665
	5·00	2·565	8·80	6·15	12·60	11·25	0·150	0·590
Methylcellulose	0·50	1·172	1·00	1·00	1·69	1·10	1·250	1·595
	1·00	1·469	2·00	1·45	3·06	—	0·910	—
	2·00	1·730	3·50	1·85	4·25	2·05	0·640	0·500
	2·50	1·862	6·45	3·05	5·75	6·05	0·350	0·275
	3·00	1·778	10·25	4·45	9·88	13·30	0·245	0·445

contact between the solid and liquid (Pilpel et al 1978). As expected, it is now observed that t_{50}, t_{90} and t_1 show good correlations with D (Fig. 4 and Table 3). The change from k_1 to k_2 at time t_1 is attributable to a change in the surface area due to break-up of the tablets into fragments (Kitazawa et al 1975). Although a good correlation between D and t_1 was observed, the two times were not the same as can be seen from Table 1. In general the disintegration times of tablets containing PVP and gelatin were less than their t_1 times. This agrees with the results obtained by Esezobo & Pilpel (1977) on uncoated oxytetracycline tablets and can be attributed to the greater agitation employed in the

Table 2. Values of the cosine of contact angles and adhesion tension of water on metronidazole tablets.

		Water (saturated with the basic formulation)			
Binder	Concn of binder (% w/w)	Drop height, h (cm)	Porosity	cos θ	AT ($mN\,m^{-1}$)
	0·00	0·1090	0·095	0·823	59·0
PVP	1·00	0·1360	0·099	0·776	55·6
	2·00	0·1635	0·084	0·729	52·3
	3·00	0·1770	0·075	0·705	50·6
	5·00	0·1935	0·067	0·675	48·4
	7·50	0·3130	0·059	0·400	28·7
	10·00	0·3510	0·057	0·279	20·0
Gelatin	0·25	0·1240	0·088	0·798	57·2
	0·50	0·1450	0·088	0·761	54·6
	1·00	0·1700	0·084	0·717	51·4
	2·00	0·1790	0·087	0·699	50·1
	3·00	0·2060	0·084	0·653	46·8
	5·00	0·3095	0·077	0·405	29·0
Methylcellulose	0·50	0·1455	0·090	0·760	54·5
	1·00	0·1820	0·089	0·693	49·7
	2·00	0·2130	0·092	0·632	45·3
	2·50	0·2710	0·082	0·505	36·2
	3·00	0·3470	0·084	0·283	20·3

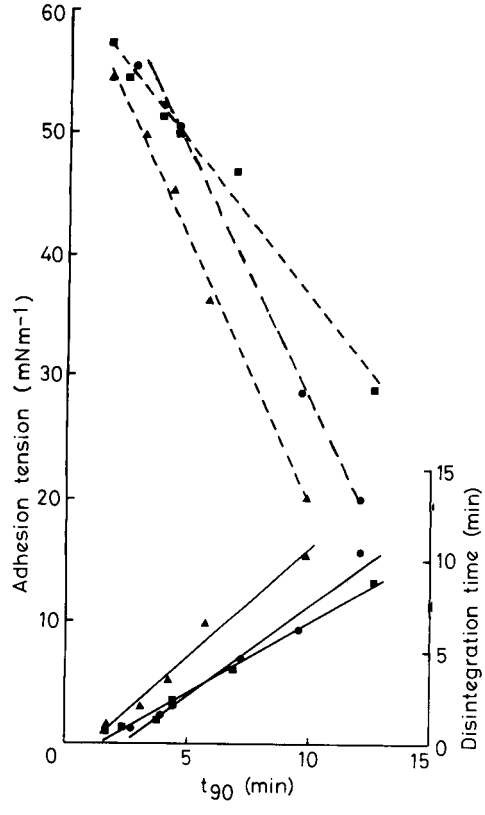

FIG. 4. Correlations of t_{90} (min) of metronidazole tablets ($P_f = 0{\cdot}90$) containing between 0·25–10·00% w/w of binders with their disintegration times (min), ——, and with the adhesion tension ($mN\ m^{-1}$) of water on the tablets, – – – – –. ●, PVP; ■, gelatin; ▲, methylcellulose.

Table 3. Correlations between various parameters of disintegration, dissolution and wettability of metronidazole tablets.

Ordinate	Abscissa	Binder	Equation for best fitting line	r
t_{50}	D	PVP	$t_{50} = 0{\cdot}53\,D + 1{\cdot}10$	0·992
		Gelatin	$t_{50} = 0{\cdot}62\,D + 0{\cdot}99$	0·979
		Methylcellulose	$t_{50} = 0{\cdot}37\,D + 0{\cdot}64$	0·999
D	t_{90}	PVP	$D = 0{\cdot}98\,t_{90} - 2{\cdot}22$	0·987
		Gelatin	$D = 0{\cdot}77\,t_{90} - 1{\cdot}03$	0·994
		Methylcellulose	$D = 1{\cdot}18\,t_{90} - 1{\cdot}17$	0·990
t_1	D	PVP	$t_1 = 0{\cdot}86\,D + 1{\cdot}10$	0·962
		Gelatin	$t_1 = 1{\cdot}21\,D + 0{\cdot}53$	0·991
		Methylcellulose	$t_1 = 1{\cdot}35\,D - 1{\cdot}55$	0·971
AT	D	PVP	$AT = -3{\cdot}83\,D + 59{\cdot}11$	−0·955
		Gelatin	$AT = -3{\cdot}20\,D + 57{\cdot}85$	−0·987
		Methylcellulose	$AT = -3{\cdot}59\,D + 57{\cdot}84$	−0·997
AT	t_{50}	PVP	$AT = -7{\cdot}34\,t_{50} + 67{\cdot}36$	−0·975
		Gelatin	$AT = -4{\cdot}89\,t_{50} + 62{\cdot}21$	−0·959
		Methylcellulose	$AT = -9{\cdot}64\,t_{50} + 63{\cdot}96$	−0·997
AT	t_{90}	PVP	$AT = -3{\cdot}12\,t_{90} + 64{\cdot}07$	−0·951
		Gelatin	$AT = -2{\cdot}48\,t_{90} + 61{\cdot}28$	−0·991
		Methylcellulose	$AT = -4{\cdot}27\,t_{90} + 62{\cdot}25$	−0·997
AT	t_1	PVP	$AT = -4{\cdot}37\,t_1 + 63{\cdot}59$	−0·974
		Gelatin	$AT = -2{\cdot}60\,t_1 + 59{\cdot}07$	−0·980
		Methylcellulose	$AT = -2{\cdot}57\,t_1 + 53{\cdot}53$	−0·978

disintegration test than in the dissolution test. For tablets containing methylcellulose, however, the pattern was less clear cut. In some cases $D < t_1$ and in other cases $D > t_1$. This is possibly due to the various roles that methylcellulose can play in tablet formulations. On coming into contact with water it first swells and then produces a gel. It is therefore used in various amounts both as a binding agent and as a disintegrant or disintegrant activator to control the rate at which drug is released from a tablet (Huber et al 1966; Mendes & Roy 1979; Shangraw et al 1980), the release rate depending considerably on the amount of methylcellulose used.

The good correlations observed between D, t_{50}, t_{90} and t_1 and the AT values of water (Fig. 4 and Table 3) can probably be ascribed to the fact that penetration of liquid into the capillaries of the tablets plays an important role in the processes of disintegration and dissolution (Jones 1981; Alkan & Groves 1982). Binding agents reduce the size and number and change the shapes of capillary spaces between the particles which are contributing to the transport of water. This explains the observed decrease in the AT of water on the tablets with increase in binder content (Table 2). Penetration of water is due to the pressure difference, ΔP, which exists across the entrance to each capillary

$$\Delta P = \frac{\gamma \cos\theta}{m} \text{ (Carman 1941)} \qquad (5)$$

where γ is the surface tension of water, θ is its contact angle on the capillary surface and m is the ratio of the cross-sectional area of the capillary to its perimeter. Since AT is $\gamma \cos\theta$, then (Carman 1941)

$$\Delta P = \frac{AT}{m} \qquad (6)$$

Obviously, the penetration decreases when ΔP decreases, i.e. when AT decreases. It may be concluded that measurements of the adhesion tension of water on tablet surfaces can be used to monitor the effects that different binding agents will have on the drug release characteristics of particular tablets. However, some account may need to be taken of the way in which AT may change as increasing amounts of the drug dissolve.

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