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EVALUATION OF COMMERCIAL METRONIDAZOLE TABLETS

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ABSTRACT

Six commercial brands of metronidazole tablets from different manufacturers were elected for this study. The tablets were evaluated using the official and non-official tests of U.S.P. XX. These tests include: uniformity of weight, hardness, friability, disintegration time and dissolution rate. The results obtained showed that most of these brands passed the U.S.P. requirements. The dissolution rate studies showed a great differences in drug release characteristics between brands and also between batches of the same brand. Studies on drug content for each metronidazole brand showed a great variation between the brands and to a less extent within the different batches of the same brand. For the intense bitter taste of metronidazole, a trial was done to

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prepare it in the form of capsule. The dissolution rate of such capsule was much better than all the commercial tablets studied.

INTRODUCTION

Metronidazole [2-(2-methyl-5-nitroimidazole-1-yl) ethanol] is an antiprotazoal agent that has been widely used for many years in the oral treatment of trichomoniasis and amoebiasis and in the prophylaxis and treatment of anaerobic infections (1-3). Tablets of metronidazole were marketed by different manufacturers under different trade names.

Recent publications have pointed out wide variation in drug absorption from tablets produced by various manufacturers (4-7). Failure to maintain uniform dosage and bioavailability due to poor product design and improper manufacturing techniques account for these variations (8). Maintenance of uniform drug content and its full availability appears to be difficult when low levels of drugs are required (9). Official compendia have recognized the vital significance of maintaining uniform dosage and availability of drugs and have set up specifications that should be met. In the present paper, six commercial brands of metronidazole tablets (which were available in the Egyptian merket) were evaluated according to the U.S.P. official and nonofficial tests.

EXPERIMENTAL

Materials

Three different lot numbers of four tablet brands and one single available batch of two imported brands, each containing 250 mgm metronidazole (obtained from the merket) were used in this study.
Metronidazole powder (supplied by Alex. Co., Egypt) and hydrochloric acid 32% (E.Merck, Darmstadt), were also used in this study.

Apparatus

Erweka disintegration apparatus, type ZT4; Erweka hardness apparatus, type TB 24; Roche friabilator, Erweka, type TA 3R; Vernier, FWP, Poland; Unicam SP 1800 U.V. Spectrophotometer and Dissolution apparatus (U.S.P. XX) were employed.

Methods

Evaluation of Tablets

Tablets were evaluated by the official and non-official tests according to the U.S.P. XX (43). These tests include: uniformity of weight, hardness, friability, disintegration time and dissolution rate: (U.S.P. XX procedure).

Determination of Drug Content

The amount of active ingredient in a single tablet

was assayed spectrophotometrically at 278 nm and the average of five determinations was calculated.

RESULTS AND DISCUSSION

The results of tests of the uniformity of weight of the six commercial brands of metronidazole tablets are shown in Fig. 1. The weight of each batch of tablets was represented by a bar indicating at its ends the lower and upper values of the tablets weights. Also the dotted lines expressed the calculated upper and lower limits of variation for each batch of tablets according to the U.S.P. XX (43). Examination of the data indicated that all the batches of the studied brands passed the U.S.P. test except two batches of brand A (A_1&A_3). However, these passed batches showed a marked interlot variation in the weights of their tablets. These results were reflected by values of the standard deviation of weight uniformity (Table 1). This variation in tablet weight could be attributed to non-uniform filling of the discs caused by variations in many parameters such as granule size, distribution, bulk density and flow properties of the granules (10,11). It was reported that the changes in tablet thickness manifested a problem in the flow properties of granules (12). Table 1 shows interlot variation in tablet thickness between some of the commercial brands. The thickness ranged from 4.28 -

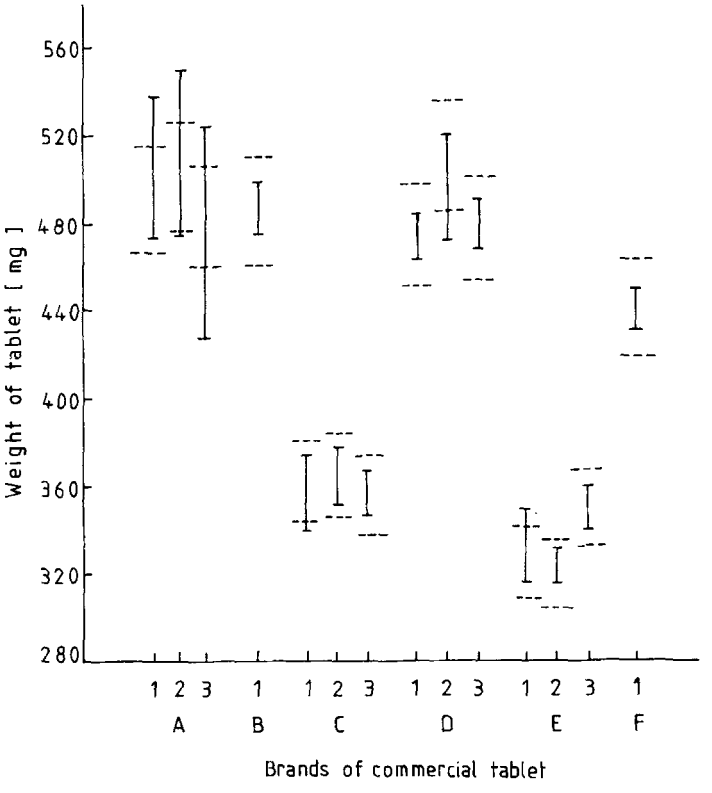

FIGURE 1. Uniformity of weight of different batches of marketed metronidazole tablets.

- - - - Upper and lower limits for each batch of tablets.

I Weight variation for each batch of tablets.

4.74 for A_1, i.e. a thickness variation of 10.8% which is reflected by a failure to obey the U.S.P. requirement for weight uniformity.

Resistance to breaking, more commonly referred to as hardness, was one of the most important parameters measured as indices of a pharmaceutical tablet quality (13-15).

TABLE 1

Evaluation of the Commercial Metronidazole Tablets

Brand	Standard deviation of weight (mg)	Thickness*** range (mm)	Hardness** range (kg)	Friability* (%)	H.F.R.	Disintegration time (m)
A_1	± 1.92	4.28-4.74	9.60- 12.50	0.040	271.00	13
A_2	± 1.96	4.26-4.77	5.90- 10.75	0.039	204.36	11
A_3	± 2.16	4.15-4.52	9.00- 11.25	0.040	254.50	10
B	± 7.78	4.42-4.62	11.75- 13.50	1.482	8.49	15
C_1	± 8.34	3.04-3.23	1.75- 3.75	8.123	0.36	3
C_2	± 7.38	3.29-3.52	6.50- 9.20	0.538	14.57	6
C_3	± 5.85	3.25-3.48	4.50- 6.50	3.746	1.52	4
D_1	± 4.50	3.66-3.79	8.10- 10.70	3.054	3.03	3
D_2	± 1.02	3.68-3.79	8.50- 10.75	4.652	2.06	3
D_3	± 7.54	4.02-4.26	7.50- 13.75	2.675	4.01	3
E_1	± 8.73	3.79-4.24	5.75- 10.75	0.185	44.22	9
E_2	± 5.61	4.12-4.37	2.50- 7.50	12.454	0.43	6
E_3	± 6.19	4.19-4.34	4.00- 7.00	0.112	50.27	5
F	± 5.45	4.17-4.31	13.50->15.00	0.045	333.33	8

* Each is an average of 5 determinations
** Each is an average of 10 determinations
*** Each is an average of 20 determinations

Friability, on the other hand, was related to the strength of the tablet and its ability to withstand abuse during normal handling, packaging and shipping (16). Most of the commercial brands studied, showed a satisfactory values for hardness range except C_1 and E_2. These were in accordance with the friability test results obtained where batches of low hardness values had high percentage friability. Tablets of C_1, C_3, E_2 and D brands failed to pass the U.S.P. requirement for friability test.

Mendes and Brannon (17) stated that a binder should serve two useful purposes, i.e., to increase hardness and decrease friability while not interfering with tablet disintegration or drug availability. Consequently, if the hardness value and the friability value could be combined to yield a single number which increases as the hardness increases or the friability decreases, this would provide an arbitrary rating scale by which various binders could be compared. It was decided that this could be accomplished by dividing the hardness value by the friability value. This would be given a number,which could be called "hardness-friability ratio (H.F.R.)". As expected, batches C_1 & E_2 had the smallest H.F.R. (0.36 & 0.43 respectively) of all the studied brands.

Hardness has been associated with other properties

such as density and porosity, all of which affect the disintegration range. Interlot variation in the disintegration time of these commercial metronidazole brands was in the following discending order: B > A > E > F > C > D.

Formulation and manufacturing processes can superimpose significant effects on the dissolution characteristics of the active ingredients in tablets (18). It should be noted, however, that the rates of the process of dissolution are all dependent upon the composition and method of preparation of the dosage form. These are all largely dependent upon pharmaceutical factors which the formulation can alter (19). There is also adequate evidences to conclude that the rate at which a drug dissolves from its intact or fragmented dosage forms in the human gastrointestinal tract, often partially or completely controls the rate at which the drug appears in blood. There is also adequate evidence to conclude that in many cases, in-vitro rate of dissolution test results can be used to explain observed differences in results obtained in animals and human subjects or patients(20-26). Therefore, the dissolution rates of different batches of six commercial brands of metronidazole tablets namely, A, B, C, D, E & F were studied.

Fig. 2 shows the dissolution pattern of metronida-

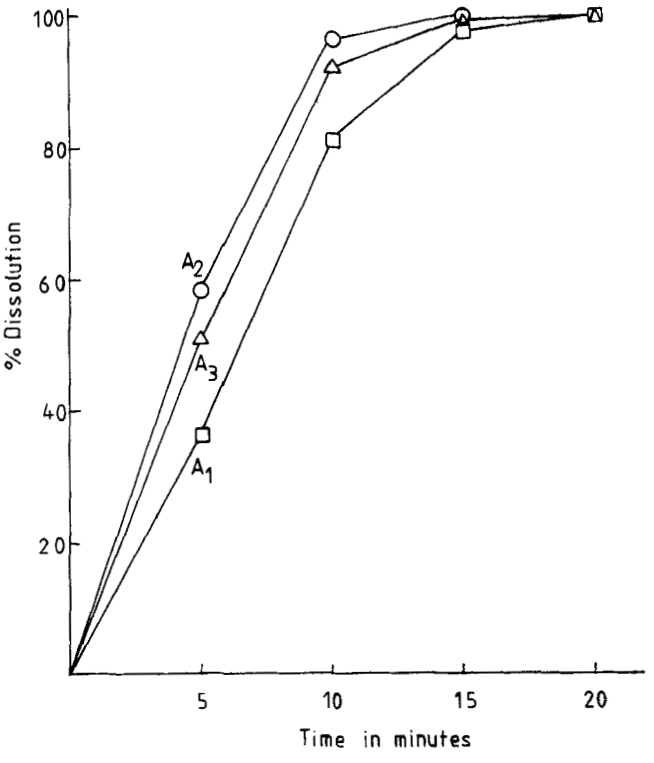

FIGURE 2. Dissolution of metronidazole tablets (Brand A) in 0.1N HCl at 37°C.

zole from the different batches of A. The results showed different dissolution rates in the following order $A_2 > A_3 > A_1$. The dissolution rates of the different batches of A showed a regular dissolution behaviour, i.e. very small deviation of the three tablets from their average dissolution rate. The standard deviations of A_1, A_2 and A_3 at t_{15} (% dissolution after 15 minutes) were 3.6, zero and 1.4 respectively.

Fig. 3 shows the dissolution rate of metronidazole

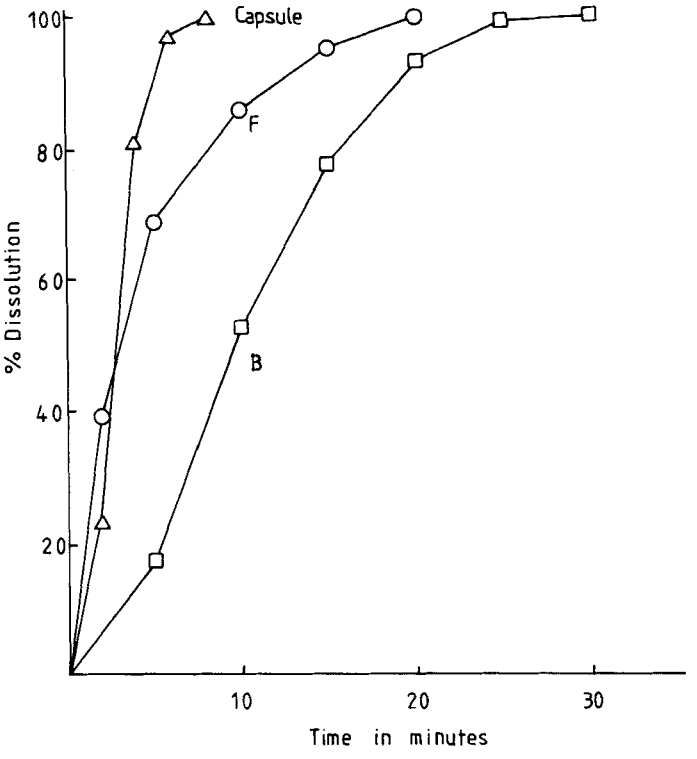

FIGURE 3. Dissolution of metronidazole tablets (Brands B & F) and capsule in 0.1N HCl at 37°C.

from the brands B and F. These two brands are imported to the Egyptian market and they were only available as single batch of each. The results illustrated better dissolution rate for brand F than brand B. The standard deviations of B and F at t_{15} were 9.7 and 4.6 respectively.

Patient acceptance for metronidazole is rather low because of its intense bitter taste. An attempt was made here to fill 250 mg metronidazole in hard gelatin capsule

size 1 for masking this taste. The dissolution pattern of three capsules was studied and the average of these results was shown in Fig. 3. The average dissolution rate of these capsules was high. The reason for higher dissolution from capsules than from tablets were most likely due to the shorter disintegration time of capsules than that of tablets. This results recommended the use of capsule instead of tablet as a suitable pharmaceutical dosage form for metronidazole.

Fig. 4 shows the dissolution of metronidazole from the different batches of C. Different dissolution profiles in the order of $C_1 > C_3 > C_2$ were obtained. Of all the studied metronidazole tablets, the dissolution rates of the different batches of C were the highest. Therefore, the standard deviations of C_1, C_2 and C_3 were calculated at t_{10} instead of t_{15} (zero, 0.6 & zero respectively). These standard deviations showed the smallest difference between each other, i.e., brand C had the best regular dissolution between its batches over all the other brands.

The dissolution rates of metronidazole from the different batches of D are shown in Fig. 5. This product has also a high dissolution rate and therefore the standard deviations for its batches D_1, D_2 and D_3 were calculated at t_{10} (3.1, 1.6 and 0.6 respectively). The

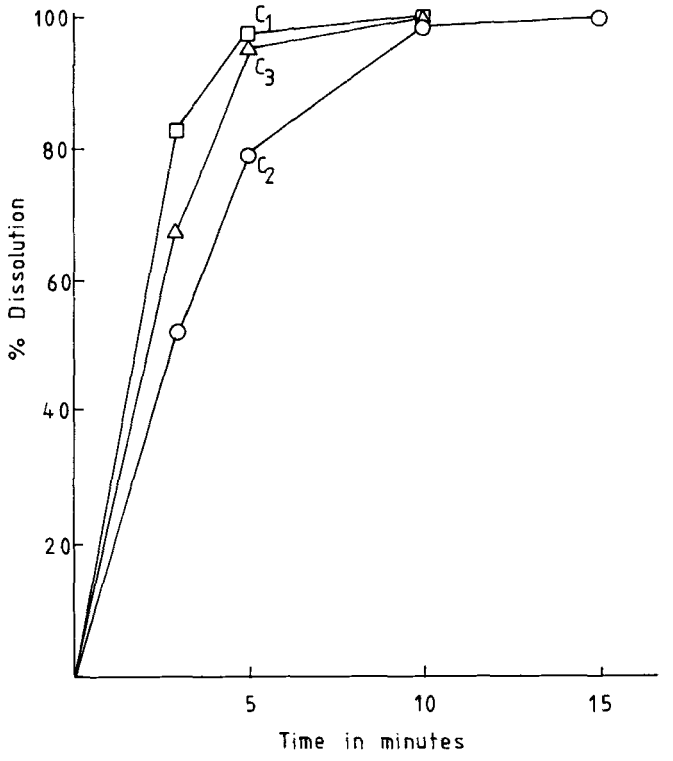

FIGURE 4. Dissolution of metronidazole tablets (Brand C) in 0.1N HCl at 37°C.

dissolution rates were in the following order

$D_3 > D_2 > D_1$.

Fig. 6 shows the dissolution rates from E_1, E_2 and E_3 batches. E_3 exhibited a higher dissolution rate than E_1 and E_2. On the other hand, E_2 showed a higher dissolution rate than E_1. Concerning the standard deviations, E_1 showed the highest irregular dissolution behaviour in all the studied commercial brands. The standard deviations of E_1, E_2 and E_3 at t_{15} were 19.3, 3.5 and 1.2 respectively.

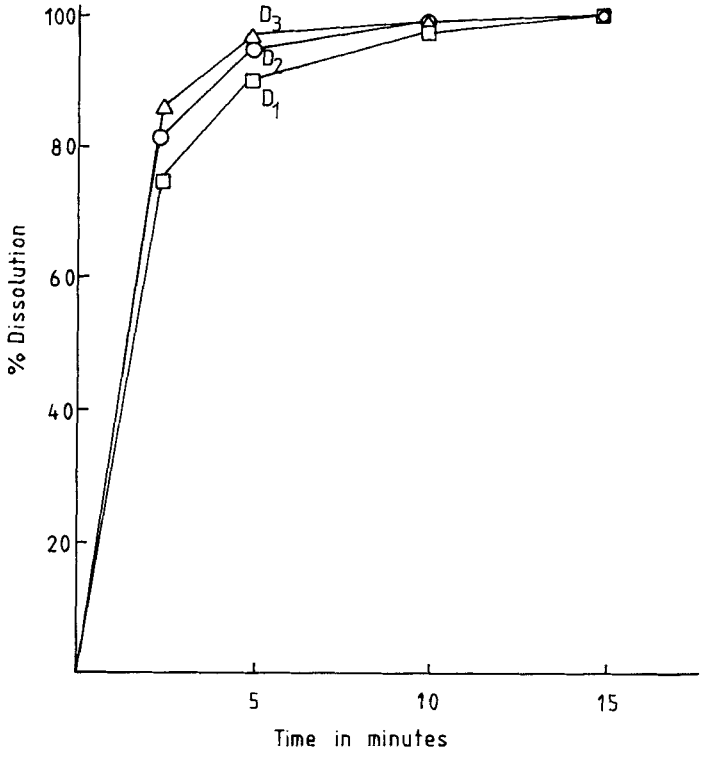

FIGURE 5. Dissolution of metronidazole tablets (Brand D) in 0.1N HCl at 37°C.

These variations in the dissolution rate of the studied commercial brands of metronidazole tablets could be referred to many variables. Some of these variables were the amount and type of diluent (28,29), binder (30-32), disintegrant (29,33), lubricant (34-36), and other adjuvants (37). The size of granules (35),38), the method of incorporation of the ingredients, the compressional force and the speed of compression (38,39-42)were also among the factors leading to the large variations in the dissolution rates.

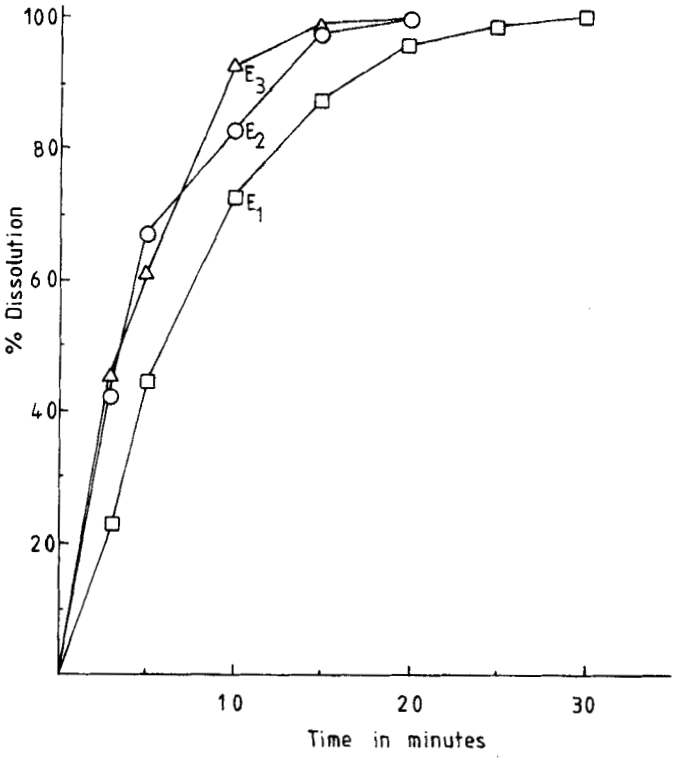

FIGURE 6. Dissolution of metronidazole tablets (Brand E) in 0.1N HCl at 37°C.

Finally, the metronidazole content in each batch of tablets was evaluated (Table 2). It has been found that all the studied tablets contained lower amounts of drug than the labelled one (250 mgm). This drop in drug content for these commercial metronidazole tablets could be referred to incorrect calculations, wrong weighing and/or improper mixing of the active ingredient during the tablet manufacturing processes.

Table 2 also showed that all the studied commercial

TABLE 2

Drug Contents of Commercial Metronidazole Tablets

Brand	% Drug Content*	Standard deviation
A_1	87.6	± 1.3
A_2	89.0	± 2.4
A_3	92.9	± 1.0
B	90.6	± 1.1
C_1	87.9	± 3.9
C_2	90.4	± 0.3
C_3	85.2	± 2.2
D_1	98.6	± 6.4
D_2	94.0	± 3.1
D_3	96.9	± 0.1
E_1	79.3	± 2.9
E_2	85.8	± 2.2
E_3	88.3	± 2.7
F	87.2	± 1.2

* Each in an average of five determinations

brands passed the U.S.P. XX requirement for drug content except E_1. The standard deviations for all the batches were calculated. Batches of C_2 and D_3 showed an excellent regularity for their drug contents,i.e., a small deviation from the average drug content. On the other hand, D_1 showed the highest standard deviation,i.e., a large variations between the drug contents of its tablets.

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