Bull. Pharm. Sci. Assiut University
Vol. 10. Part 2, PP. 123 - 138 (1987).

Short Communication.

DISSOLUTION BEHAVIOUR OF METRONIDAZOLE TABLETS

E.A. Ibrahim, S.S. Tous, T.H.El-Faham and M.A.Hassan.

Dept. of Pharmaceutics, Faculty of Pharmacy, Assiut University
Assiut, Egypt.

ABSTRACT

The dissolution behaviour of metronidazole tablets from three locally manufactured brands on the Egyptian market was studied. Four batches from each brand were collected from the market. The compliance of the tablets collected to the USP XX requirements was evaluated. Some batches from certain brands did not pass the USP XX requirements for disintegration time, potency and weight variation. The USP XX paddle method was, used for the dissolution studies. 0.1 N HCl at 37^{0}C was used as the dissolution medium. Nine tablets from each batch were considered in the dissolution study. The results revealed significant differences among and within the batches of the same brand for the percent metronidazole dissolved after 10, 30 and 105 minutes at $p < 0.1$ significance level. Moreover a significant difference was found to exist between different brands. The dissolution rate of drug powder was found to be higher than that of tablets.

Furthermore, the drug powder filled into capsules showed higher dissolution behaviour than tablets and lesser than drug powder. In addition, the bioavailability of the drug powder filled into capsules as well as tablets, was studied. The results revealed that there was a correlation between the in vitro dissolution rate of the drug and its in vivo absorption data.

INTRODUCTION

Metronidazole is used in medicin as an antiprotozoal agent. Moreover it has antibacteria actions and is effective against trichomonas vaginalis an other protozoa including.: Entamoeba histolytica , . Giardia lamblia and against anaerobic bacteria[1,2]. The use of metronidazole is associated with some controversy regarding its carcinogenicity in some animals and mutagenicity in bacteria[1]. Recently, it has been found that, metronidazole as a radiosensitizer, is of possible clinical use in cancer chemotherapy[3]. Inspite of its side effects, metronidazole is often the drug of choice for the treatment of many infections. It is available as, suppositories, suspensions , tablets and vaginal tablets[1]. Attempts have been made to microencapsulate metronidazole, to mask its bitter taste[4]. The microcapsules have been compressed into tablets which were harder and had lower friability values than those prepared from uncoated granules[4]. The influence of binding agents on the release of metronidazole tablets was investigated[5]. It has been found that tablets containing PVP and drug with particle size 1.75 um (in lactose mixture) gave optimum results[5].

The bioavailability of commercial metronidazole formulations has been investigated[6]. Comparison was made between 8 commercial tablets and a solution. The tablets were found to be within the compendial standard limits and no significant differences was found in the area under the plasma concentration-time curve. The solution gave significantly lower extent of bioavailability than the reference tablet[6]. On the other hand, the in-vitro evaluation of six commercial brands of metronidazole tablets from different manufacturers has been performed[7]. The results obtained showed that most of the brands passed the USP requirements. However, there was difference in

drug release characteristics between brands and also between batches of the same brand[7].

In the present study three brands of locally manufactured tablets were collected from Egyptian market. Four batches from each brand were evaluated for compliance with the USP XX standards for weight variation, potency and disintegration time. The USP XX does not include a dissolution requirements for metronidazole tablets[*]. So, it was aimed at exploring the dissolution behaviour of the drug from its tablet form and its correlation with the bioavilability characteristics of the tablets.

EXPERIMENTAL

Materials :

Metronidazole Powder (El-Nile Co., Egypt), metronidazole tablets (El-Nile Co., El-Kahira and Alexandria Co., Egypt). Hydrochloric acid, glacial acetic acid, perchloric acid, zinc dust, brilliant green, vanillin were used. All chemicals and reagents were either of analytical or pharmaceutical grades and were used without further purification.

Methods :

Weight variation, disintegration time and drug content of tablets were performed following the USP XX[11].

Dissolution Studies :

The dissolution rate of metronidazole powder and tablets were determined using USP XX paddle method. 250 mg powder or one tablet was introduced into 500 ml 0.1 N HCl adjusted at 37 $\pm$ 0.5 ^{o}C using

---

(*) Now, the USP XXI describes a dissolution test for Metronidazole tablets. The dissolution medium is the same used by us, but the rate of stirring is doubled.

stirring rate of 50 rpm. Aliquot portions of about 5 ml were withdrawn at specified time intervals . The samples were measured at 278 nm after appropriate dilution with 0.1 HCl.

Bioavailability Studies :

Five healthy volunteers, two females and three males were participated in the study. The age of the individuals ranged from 26-36 years (mean 32) and the body weight from 56-68 kg (mean 63.5). Participants were required to observe normal diet and follow normal sleeping habits. For each study, the bladder was voided and the urine was collected to serve as blank specimen. Two tablets or two drug powder-filled capsules (each containing 250 mg metronidazole) were administered to the five subjects with a glass of water in the morning after an overnight fasting. Food but not water was witheld for one hour postmedication . The participants received other preparations at weekly intervals. . Urine samples were collected at 1,2, 4, 6 hours time intervals and cumulative volume of urine excreted from 6-24 hrs. The total amounts of metronidazole and metabolites excreted were determined colorimetrically[12] . Four ml of each urine sample were transfered to 25- ml beaker. About 0.4 gm zinc dust and 2 ml hydrochloric acid were added. The reaction was left till the effervescence ceased. The volume was completed to 10 ml with distilled water. The mixture was filtered through filter paper, the first portion of the filtrate was rejected. One ml of the filtrate was transfered into 10-ml volumetric flask. one ml vanillin solution (1 % w/v) was added, the mixture was left for 2 hours and the volume was completed to 10 ml with distilled water. The yellow colour obtained was measured at 408 nm, against blank similarly prepared.

RESULTS AND DISCUSSION

Some batches from certain brands did not pass the USP XX requirements for weight variation, potency and disintegration time. All batches of three brands pass the USP XX test for weight variation except one

batch of flagicure (batch No. 822616). Since, the weights of three tablets from this batch were deviated, than the limited percentage difference (5 %), from the average weight (0.5025 gm). Two of them were more and one was less than the limited value. The USP XX states that metronidazole tablets contain not less than 95% and not more than 105 % of the labeled amount of $C_6H_9N_3O_3$. From table 1 it is clearly obvious that the potency of the tablets from different brands was within the USP XX specifications except flagicure. Since, three batches having higher potency than the specified value. The disintegration time of all tablets from different brands was within the limits of USP XX except one batch of flagicure (822616). Three tablets from this batch disintegrate within 21-27 min. i.e. higher disintegration time than the specified limit (15 minutes).

The previously mentioned results may be reflected on the dissolution behaviour of the drug, since the dissolution data involve factors related to disintegration rate of the dosage form. Furthermore, in many cases, in-vitro rate of dissolution test results, could be used to explain observed difference in results obtained in animal or human subjects[8-10]. The dissolution behaviour of metronidazole tablets from the three brands was studied . Nine tablets from each were considered in the dissolution study to depict the intrabatch variations. Four batches from each brand were included to shed some light.on the interbatch variation. Moreover, the comparison was made also between the three brands.

Figure 1 illustrates the dissolution behaviour of metronidazole tablets from different brands compared to that of the drug powder. It was clearly obvious that the dissolution rate of drug powder was much higher than tablets. The percent drug dissoluted after 8 minutes from powder was 100% while the highest amount dissoluted in case of tablets was 61 % after 10 minutes , that is because, tablets need longer time for its disintegration.

From table 2 it is obvious that batch No. 11047 of flagyl tablets shows the highest dissolution rate followed in order by 112196, 112199 and 10549. The highest percent dissoluted of metronidazole from this brand was found to be 69.4 % after 30 minutes and not more than 89.02 % after 105 minutes. Also from table 2, it is obvious that the highest dissolution rate of flagicure tablets was exhibited by batch No. 822615 followed in order by 823119, 822616 and 822301. The last two batches were nearly identical in the dissolution rate. The highest percent dissoluted of metronidazole was found to be 68.2 after 30 minutes and not more than 86.68 % after 105 minutes. The dissolution behaviour of four batches from flazol brand was studied. Three batches viz., 3146, 3857 and 3861 of this brand showed the same dissolution pattern and of higher rate than batch No. 1027. The highest amount dissoluted from tablets of this brand was 92.72 after 30 minutes and 97.48 after 105 minutes. Figure 1. Compares the dissolution behaviour of metronidazole from different brands. Flazol tablets gave the highest dissolution rate followed in order by flagyl and flagicure. The results obtained was not in agreement with the results obtained by Gadalla et al[7], who reported that 100 % metronidazole was dissoluted from all tablets after 20-30 minutes. While in our study non of the tablets reached 100 % dissolution even after 105 minutes. The discrepancy in results may be due to the difference in brands and batch selection.

The above mentioned results were summarized in tables 2 and 3. The values of the parameters Q_{10} min, Q_{30} min and Q_{105} min (% drug dissoluted after 10, 30 and 105 minutes) were statistically analysed to allow the expressions of the intrabatch, interbatch and interbrand variations in a quantitative manner. The results revealed that, there was a significant variation among and within batches of the same brand for the percent metronidazole dissoluted after 10,30 and 105 minutes, at 0.1 significance level. Also, a significant difference was found to exist between different brands. Generally, the s.d's among and within batches of flazol were the least values (tables 2 & 3) indicating the least intra and interbatch variation in flazol tablets. The higher values of s.d's as shown in table 3 indicating that there was interbrand variation. The variation was clearly observed at the begining of the dissolution period i.e. after 10 and 30 minutes. It was worthy to note that, the variation among and within tablets did exist even between tablets that pass the USP disintegration test.

To explore the importance of in vitro dissolution studies in predicting the bioavailability of the drug, it was necessary to compare the bioavailability of the brands that show the lowest and the highest dissolution rates (flazol and flagicure). Also, the comparison was made between drug powder, that exhibits higher dissolution rate, and flazol tablets. The drug powder was filled into gelatin capsules for ease of administration. The dissolution rate of the drug powder filled into gelatin capsule was studied (Fig. 1). It was clearly obvious from figure 1 that the drug powder filled into gelatin capsule shows higher dissolution rate than flazol tablets and lesser than drug powder. Furthermore, the variations in the dissolution rate between capsules were lesser than all brands tested.

Figur 2, shows the mean cumulative urinary excretion profile of metronidazole. It was clearly observed that drug filled into gelatin capsule showed higher excretion rate followed by flazol and flagicure tablets, after 4 and 6 hours. After 24 hours, the excretion rate of drug filled into capsule was still the highest followed in order by flagicure and flazol tablets. Using student t-Test ($P \leq 0.05$) for comparison of the means amount excreted, the data showed significant difference after 1 and 6 hours between flazol and flagicure tablets. On the other hand there was a significant difference after 1,4, 6, and 24 hours between flazol and drug filled into gelatin capsule. The in vitro data for the amount dissolved after 10, 30,105 minutes, showed significant difference between flazol and flagicure tablets in one hand and between flazol and capsule in the other hand (Fig.1). On the basis of these results, it may be concluded that correlation exists between in vitro dissolution results obtained from this investigation and the bioavailability of metronidazole. The elimination rate constant (K) of metronidazole may then be obtained from plots of log excretion rate vs time (Fig. 3). The excretion rate constant thus obtained ranged from 0.064-0.080 hr^{-1} correspond to half life of 8.68-10.68 which is nearly within the reported range(8-9).[13]

It can be further concluded that, there was a significant variation in bioavailability between the two brands of tablets, although these brands pass the USP XX disintegration test. So, it may be suggested that a dissolution standard for metronidazole tablets, could insure adequate bioavailability of the drug than currently used disintegration test.

Table I : Drug Contents of Commercial Metronidazole tablets.

Brands	Batches	% drug Content
Flagyl.	105044	96.6 %
	112199	99.2 %
	110147	97.7 %
	112196	95.4 %
Flagicure	823119	110.6 %
	822301	108.4 %
	822616	102.9 %
	822615	112.1 %
Flazol	1027	97.9 %
	3857	96.5 %
	3146	95.8 %
	3861	100 %

Table 2 : Intra-batch variation in dissolution behaviour for metronidazole tablets from different brands

Brand	Batch No.	Dissolution Parameter	Range	mean	s.d.
Flagicure	822616	$Q_{10\ min.}$	9.8 - 38	17.93	10.58
		$Q_{30\ min.}$	30.1 - 62.5	39.35	12.183
		$Q_{105min.}$	58.5 - 91.8	71.25	14.457
	822301	$Q_{10\ min.}$	11.6 - 39.6	18.82	10.815
		$Q_{30\ min.}$	23.9 - 75.3	39.977	18.336
		$Q_{105min.}$	47.1 - 96.3	68.533	16.293
	823119	$Q_{10\ min.}$	16.9 - 31.4	22.722	5.043
		$Q_{30\ min.}$	41.6 - 54.7	47.644	4.380
		$Q_{105min.}$	81.3 - 98	86.322	5.826
	822615	$Q_{10\ min.}$	26.5 - 58.3	41.066	10.272
		$Q_{30\ min.}$	52.8 - 86.6	68.422	11.95
		$Q_{105min.}$	78.3 - 93	86.688	5.1699
Flagyl	112199	$Q_{10\ min.}$	3.5 - 47.6	16.444	13.463
		$Q_{30\ min.}$	43.3 - 84.1	62.833	15.414
		$Q_{105min.}$	79.4 - 91.3	86.2	3.872
	105044	$Q_{10\ min.}$	2 - 10.9	5.222	3.702
		$Q_{30\ min.}$	13.2 - 65.2	38.344	21.339
		$Q_{105min.}$	60 - 92.9	82.788	11.533
	11047	$Q_{10\ min.}$	3.1 - 39.5	15.755	12.075
		$Q_{30\ min.}$	33.3 - 82.9	67.288	14.788
		$Q_{105min.}$	87.1 - 91.4	89.022	3.0297
	112196	$Q_{10\ min.}$	13.2 - 35.1	22.911	8.929
		$Q_{30\ min.}$	53.1 - 84.3	69.4	11.932
		$Q_{105\ min.}$	84.7 - 92.1	88.2	2.821
Flazol	1027	$Q_{10\ min.}$	48.2 - 64	56.3	5.649
		$Q_{30\ min.}$	75.1 - 84.8	80.238	3.118
		$Q_{105\ min.}$	87.6 - 96.5	90.666	2.725
	3146	$Q_{10\ min.}$	45.8 - 83.5	65.977	13.217
		$Q_{30\ min.}$	81.0 - 97.0	92.322	4.9014
		$Q_{105\ min.}$	92.8 - 99.6	97.488	2.279
	3861	$Q_{10\ min.}$	46.2 - 63.5	55.588	7.286
		$Q_{30\ min.}$	78.6 - 93.0	88.644	4.0109
		$Q_{105\ min.}$	93.2 - 96.4	94.877	0.899
	3857	$Q_{10\ min.}$	52.2 - 72.2	60.411	7.382
		$Q_{30\ min.}$	87.2 - 96.1	92.733	2.846
		$Q_{105\ min.}$	94.0 - 98.8	96.844	1.724

Table 3 : Interbatch and interbrand variation in dissolution behaviour for Metronidazole tablets from different brands.

Brand	Dissolution Parameter	Range	mean	S D.
Flagicure	Q_{10} min.	17.9 - 41.06	25.125	10.826
	Q_{30} min.	39.35- 68.42	48.845	13.583
	Q_{105} min.	68.53- 86.68	78.195	9.655
Flagyl	Q_{10} min.	5.22- 22.9	15.08	7.317
	Q_{30} min.	38.34- 69.4	59.46	14.34
	Q_{105} min.	82.7 - 89.02	86.55	2.77
Flazol	Q_{10} min.	55.58- 65.97	59.562	4.77
	Q_{30} min.	80.28- 92.73	88.492	5.775
	Q_{105} min.	90.66- 97.48	94.962	3.075

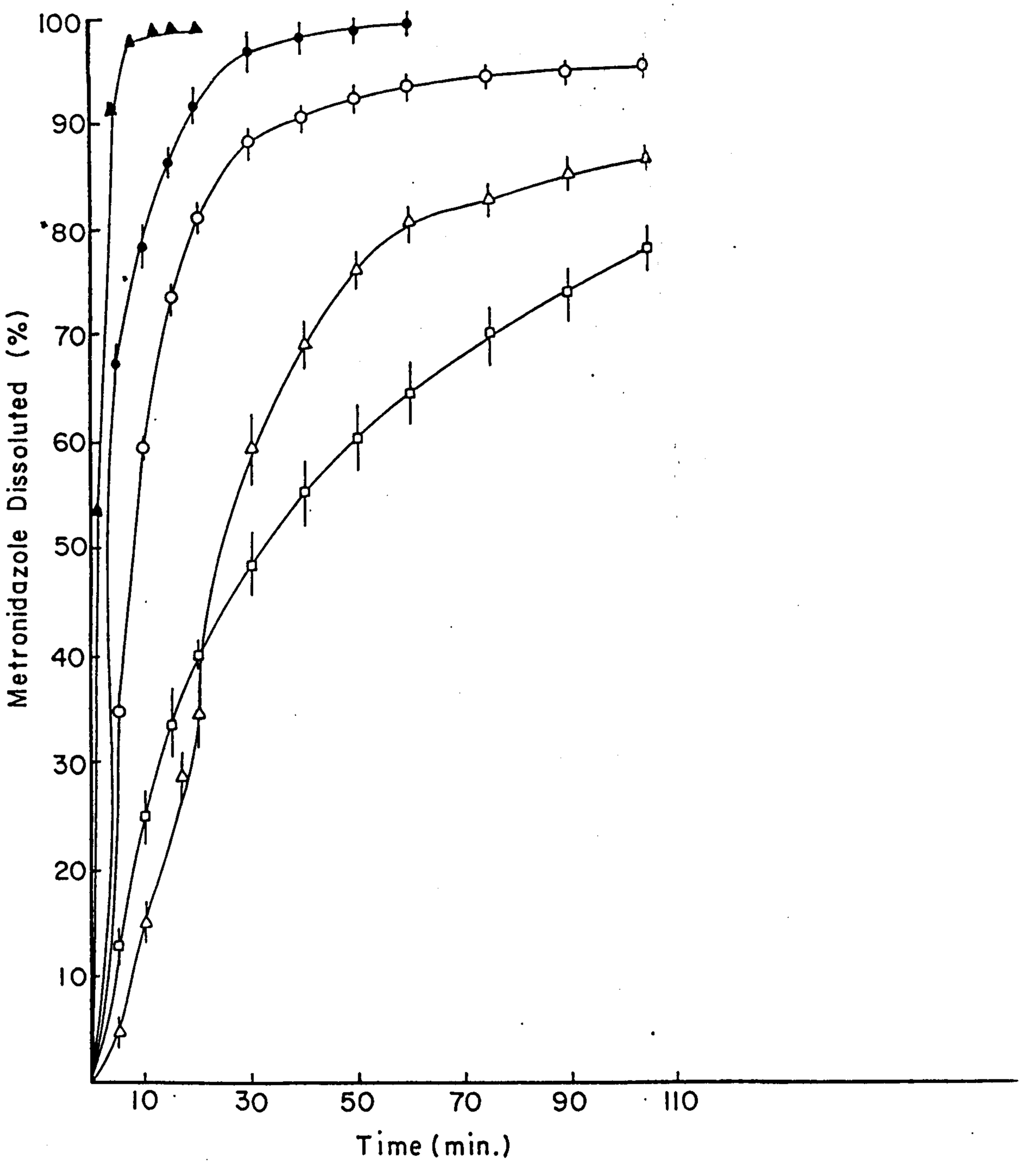

Fig.(1):Dissolution behaviour of metronidazole tablets from different brands and drug powder filled into cap

△ Flagyl □ Flagicure ○ Flazol

● Drug powder filled into capsule

▲ Drug powder

Dissolution Behaviour of Metronidazole Tablets

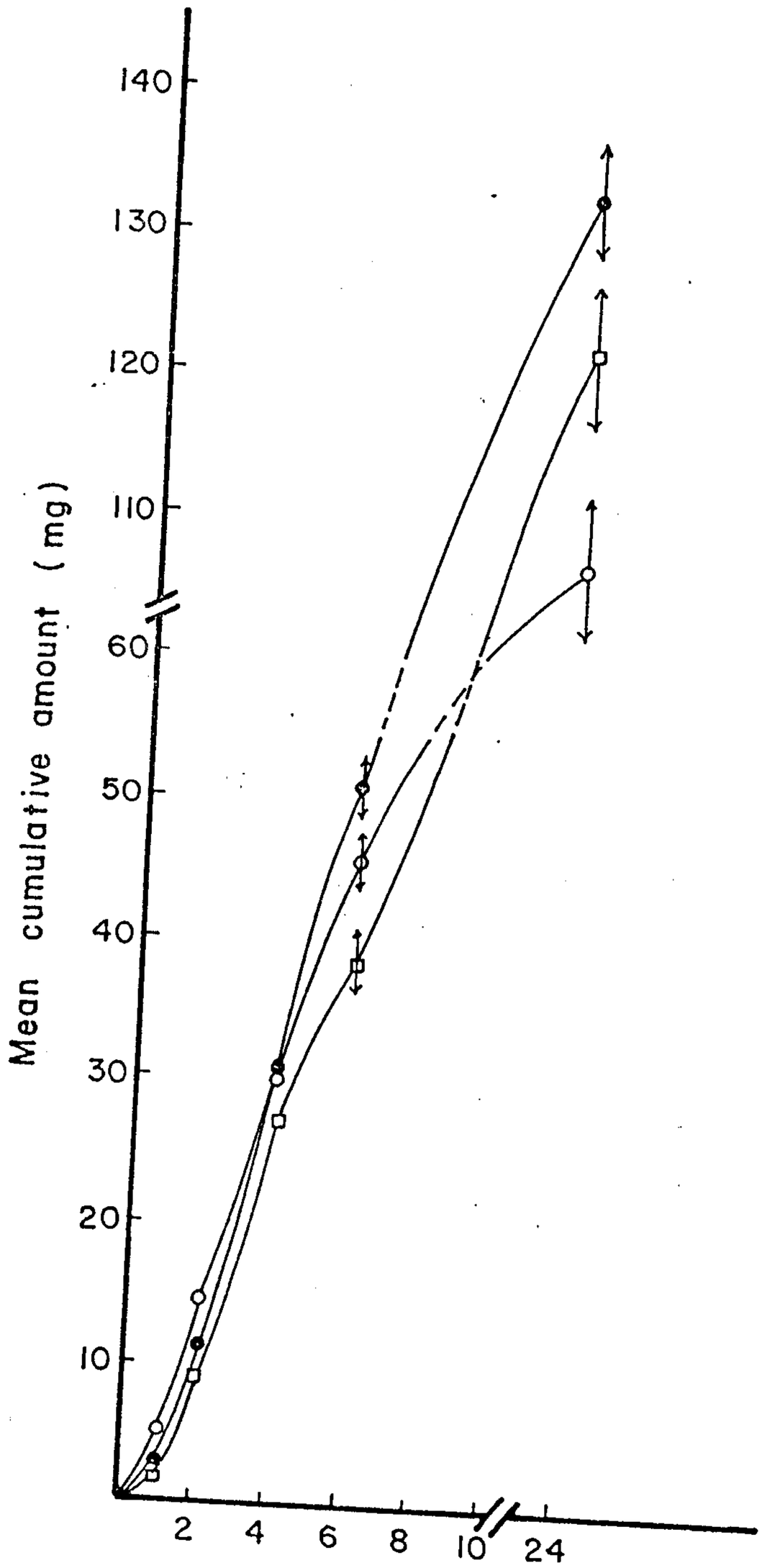

Fig.(2): Mean cumulative urinary excretion of metronidazole after oral administeration.

● Drug powder filled into capsule □ Flagicure

○ Flazol

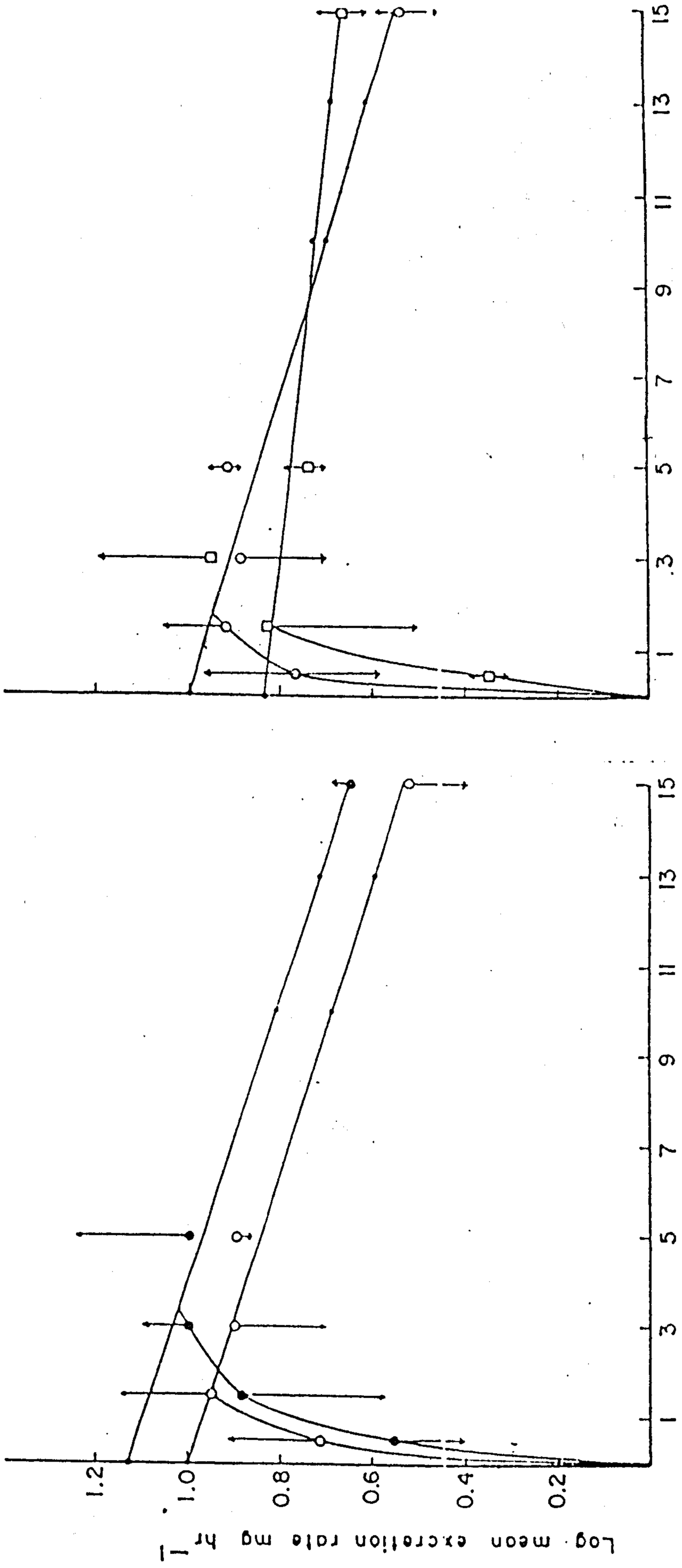

Fig.(3): Logarithmic plot of excretion rate of metronidazole against time

	o Flazol	□ Flagicure
• Drug powder filled into capsule		
K(min^{-1}):	0.0798	0.0710
$t_{\frac{1}{2}}$(min) :	8.5890	9.7600
• Drug powder filled into capsule		
K(min^{-1}):	0.0649	
$t_{\frac{1}{2}}$(min) :	10.6845	

REFERENCES

1.) R.C. Todd, "Extrapharmacopoeia : Martindale 28th ed., p. 968. The Pharmaceutical Press. London (1982).

2) R.J. MD,Mitre, E.B.Jr. Rotheram, and M.D., JAMA, 230,1168 (1974).

3) M.N., Eakins, P.J.,Convay, A.J.,Searle, T.F. Salter and R.L., Willson, Biochem. Pharmacol, 25, 1151 (1967).

4) M.R., Baichmal, and I.A., Abraham, Indian J. Pharm. Sci., 42, 48 (1980).

5.) J.A.K., Louwo, Drug Develop. and Indust. Pharm. . , 10,1085(1984).

6.) I.J., McGilveray, and J.C.K., Midha, Pharmacol. Biopharm., 16, 110 (1978).

7) M.A.F. Gadalla, A.R. Ebian, and G.M., Chaly, Drug Develop. Ind. Pharm., 10, 1097 (1984).

8.) E. Nelson, E.I., Knoechel, W.E. Hamlin, and J.C.Wagner, J.Pharm. Sci., 51, 509 (1962).

9) E., Nelson, S.Long, and J.C. Wagner, Ibid, 53, 1224 (1964).

10) J.C., Wagner, Can. J. Pharm. Sci., 1, 55 (1966).

11.) The United States Pharmacopoeia, XX (1980).

12.) N.M. Sanghavi, and H.S., Chandramohan, Indian J. Pharm.. 36, 151 (1974).

13.) A., Samu and A. Csiba, Gyogyszereszet 25, 45 (1981) Through ; C.A. 94, 162660 h (1981).

خصائص معدل ذوبان أقراص الميترونيدازول

السيد على ابراهيم ـ موزان شوقى طوس ـ تهانى حسن الفحام ـ مهاعبدالعظيم حسن

قسم الصيدلانيات ـ كلية الصيدلة ـ جامعة أسيوط

تم دراسة معدل الذوبان لاقراص الميترونيدازول ـ وقد تم الحصول على هذة الاقراص من السوق المصرى . تم جمع أربع تشغيلات من كل من ثلاث شركات محلية ـ تم تقييم هذة الاقراص تبعا لمواصفات الدستور الامريكى العشرون ـ وقد وجد أن بعض التشغيلات من شركات معينه لاتتبع المواصفات من حيث وقت التكسير والفاعلية والتباين فى الوزن .

وقد استعملت طريقة لدستور الامريكى لدراسة معدل الذوبان واستخدم حمض الايدروكلوريك ار عيارى عند درجة ٣٧°م كوسط لدراسة معدل الذوبان ـ وقد وضع تحت التجربة تسعة أقراص من كل تشغيلة .

وقد أسفرت النتائج عن وجود اختلاف احصائى معنوى بين الاقراص من ناحية وبين التشغيلات للشركة الواحدة ـ بمقارنة الكمية الزائبه من العقار بعد عشرة ،ثلاثون ،ومائه وخمس دقيقة عند درجة ثقة قدرها ٠/٠٩٠ علاوة على ذلك فقد وجد هناك اختلاف احصائى معنوى ببن الاقراص المأخوذة من الشركات المختلفة .

وقد ثبت بالتجربة أن معدل ذوبان مسحوق العقار أكثر من الاقراص وأن مسحوق العقار المعبأ فى كبسولات من الجيلاتين له معدل اذابة أكثر من الاقراص وأقل من مسحوق العقار نفسه .

علاوه على ذلك فقد تم دراسة التوافر الحيوى للاقراص ومسحوق العقار المعبأ فى كبسولات ، ووجد أن هناك علاقه مباشرة بين الدارسة المعملية لمعدل الذوبان وبين الدراسة داخل جسم الانسان .

---

received in 4/3/1987 & accepted in 7/1/1988