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A STUDY ON THE RELATIONSHIP BETWEEN DISINTEGRATION OF DIRECTLY COMPRESSED SULPHADIMIDINE TABLETS AND THEIR PHYSIOLOGICAL AVAILABILITY IN MAN.

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A study was made on the disintegration time and in vivo absorption rate of sulphadimidine tablets prepared by direct compression technique using Celutab (50% w/w) as an excipient. Tablets of greatly different disintegration times were selected for this investigation. Using urinary excretion method, it was shown that there is a relationship between disintegration time and in vivo absorption of sulphadimidine tablets, in that the tablet with faster disintegration time gives a higher absorption as indicated by the excretion rate calculated from the cummulative amount of sulphadimidine excreted.

A drug is a chemical substance that acts in biological system to preferentially give a beneficial pharmacological or chemotherapeutic effect.

For many years disintegration tests served a useful purpose in indicating the biological availability of drugs . However , these tests did not help in the appreciation of the in vivo observations since they have certain inherent faults which limit their usefulness as measures of biological availability. On the other hand, disintegration, merely measures the time required for a tablet to break into granules smaller than a given size, but it

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tells nothing about how rapidly the drug is released from these granules, a condition that is most necessary for gastrointestinal absorption[1]. As early as 1948, it was recognized by Sperandio et al.[2], that while the efficiency of a compressed tablets is, to some degree, related to the speed of disintegration, the dissolution of the drug particles is of prime importance. Thus, the disintegration tests was logical that they should be replaced by more critical tests, such as dissolution rate tests.

Despite the fundamental relationship between in vitro dissolution rate and in vivo availability, no single dissolution test can be applied to all drugs. It is therefore necessary to obtain evidence of availability of each drug in each formulation by quantitative in vivo measurements. Only when a relationship between in vivo availability and in vitro dissolution rate has been established, may the latter be used for prediction of biological availability and can,properly designed in vivo tests,be used to ensure that products are manufactured under proper pharmaceutical conditions.

Smits and Nienhuis[3], succeeded to establish a relationship between dissolution T 50% and disintegration time of sulphadimidine tablets. Van Oudtshoorn and Potgieter[4] on the other hand, found that a definite relationship appears to exist between disintegration time and dissolution rate of four commercially available brands of sulphadimidine tablets. Likewise a large number of investigations were carried out to establish a relationship between in vitro dissolution rate and in vivo absorption of a drug.[5-10]

In a study with three sulphadimidine tablets formulations with a slow, medium and fast dissolution rate respectively, Taraszka and Delor[11] found that several in vivo parameters paralleled the in vitro dissolution rate of sulphadimidine from the three formulations, but that not all the in vivo differences were as great as might be expected from the in vitro data. The in vitro method could differentiate between formulations which could not be differentated by blood levels using nine subjects. Using urinary excretion methods, Van Oudtshoorn and Patgieter[4] were able to demonstrate a correlation between in vitro dissolution rate and

in vivo absorption of sulphadimidine frcm tablets , in that a tablet with a slower dissolution rate gave a slower absorption rate.

The objective of this study was to establish what correlation, if any, exists between in vivo and disintegration data for tablet formulations of sulphadimidine prepared by direct compression.

EXPERIMENTAL

Six tablet formulations of sulphadimidine[a] prepared by direct compression technique using 50% w/w Spray-Crystallized-Maltose Dextrose (Celutab or Emdex[b]) as an excipient, were used for the bioavailability study. These formulations differ from each others according to the disintegrant used. On this basis the tested formulations were greatly different in their disintegration times Table 1. The six formulations used were:

1- Sulphadimidine tablets containing 10% w/w amberlite[c].
2- Sulphadimidine tablets containing 10% Primojel[s].
3- Sulphadimidine tablets containing 10% Meyprogat[d].
4- Sulphadimidine tablets containing 2.5% Meyprogat[d].
5- Sulphadimidine tablets containing 5% Veegum W.G.[e].
6- Sulphadimidine tablets without disintegrant.

Six healthy male subjects, aged between 24-40 years, and weighing between 60-100 Kg were used for this investigation. All subjects were refrained from any medication during and at least two weeks preceding the experiments. Fifteen tablets, 0.1 mg each, of sulphadimidine were given on an empty stomach at 8.00 a. m. with a tumbler of water of 250 ml. No food was

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a. El Nasr Chemical and Pharmaceutical Company, Cairo.
b. Celutab or Emdex, E. Mendell Co. Inc. Carmel, N.Y., U.S.A.
c. Amberlite IRP 88. Lenning Chemical Ltd., London.
d. Meyprogat 30 Information Bulletin, Meyhall Chemical AG, Kreuzlingen, Switzerland.
e. Veegum W. G, R. T. Venderbilt Co. Inc., N. Y., U.S.A.

allowed for at least two hours after the ingestion of the tablets. Blank urine was collected before the administration of sulphadimidine tablets. The urine was collected quantitatively in clean pyrex glass, amber-coloured stoppered wide mouth jars at 1, 3, 6, 9, 12 and 24 hours, or in between, after the administration of the drug. The collected urine was refrigerated immediately and assayed according to the adapted method[12] of Bratton and Marshall[13] within 24 hours after collection for total. Control experiments were similarly run for each subject but using 1.5 gm sulphadimidine powder in the packet. Each formulation was tested on the six subjects. The test was carried out in cross over manner in some instances, and at least two weeks were allowed before undertaking another experiment on the same subject.

Duplicate tests were carried out for each sample. A correction for urine blank was done by undertaking the previous procedure on blank urine. The amount of total sulphadimidine present in the aliquots was extrapolated from a derived standard curve . Results are shown in Table 2 and Figrues 1, 2.

RESULTS AND DISCUSSION

The use of the urinary excretion method to assess the physiological availability of sulphadimidine from formulations under investigation was based on the assumption that excretion rates should directly reflect the blood level, which was verified by some studies on sulpha drugs[4,11]. Urinary excretion methods have been used extensively to assess the bioavailability of several sulpha drugs[4,11], on the account of its merits, being a simpler and perhaps more accurate alternative to the use of blood level data.

The physiological availability was calculated according to Morrison et al.[14] as follows :

$$\% \frac{\% \text{ excreted from test}}{\% \text{ excreted from control}} \times 100$$

It was demonstrated from tables 1, 2 and figures 1, 2 that the 24 hr urinary excretion data indicated that the control sulphadimidine (powdered form) was readily excreted in urine in the range of 68 - 93%. While other tested tablet formulations gave a discrepancy in the amount of drug excreted along this period according to the disintegration time of each tablet. Insignificant interindividual variations was noticed in the obtained urinary excretion data which might be due to variable factors mainly protein binding for sulpha drug. It was apparent that the percent of urinary excretion of sulphadimidine was high for formulation possessing rapid disintegration and a delay in the percent excreted for that having a long time of disintegration (Table 2 and Figure 2).

Plotting the percent cummulative urinary excretion of sulphadimidine versus the disintegration time for each investigated formulation on a semilogarithmic paper yielded a linear relationship with a correlation coefficient of about 0.9 in most cases (Figure 1). Thus, a direct correlation was obtained between the bioavailability of sulphadimidine tablets and their disintegration times.

Literature reveals many cases where no correlation could be derived between disintegration times and either dissolution rates[1, 15-19], or in vivo measurements[19-23]. On the other hand, other reports showed disintegration times to be correlated with dissolution rate[15, 24-30], or they showed rank correlation with dissolution times[19, 32-33].

Schroeter et al[30] and Middleton et al[34] working on coated tablets of riboflavin, sodium p-aminosalicylate and salicylate, pointed out that there is sometimes a high degree of correlation between rate of dissolution (as reflected by the T_{50} value) and in vitro disintegration time. Hence in these cases either in vitro disintegration time or the T_{50} values will correlate reasonably well with the physiological availability values. On the other hand, Goosseus and Van Oudtshoorn[35] working on a sulphathiazole and sulphafurazole found no correlation between disintegration time and dissolution rate. Also, they concluded that there was a relationship between in vitro dissolution rate

and in vivo absorption of sulphathiazole but this relation did not exist for sulphafurazole. Mattoch and McGilveray[36] in another study on sulphamethizole found that no correlation was obtained between dissolution and absorption parameters. A similar finding was obtained by Sakr et al.[37] for sulphathiazole tablets who pointed out that no apparent correlation could be deduced between disintegration time and in vivo data.

From this study, it could be concluded that since disintegration time is the easier control test to carry out, it may be used to control the product in those cases where a correlation has been obtained between disintegration and bioavailability data.

Table I. Disintegration time of Sulphadimidine tablets Used for the Bioavailability study

Tablet	B. P. Disintegration time (minutes)			
	Distilled water		0.1 N HCl	
	Mean	C. V. %	Mean	C. V. %
1	0.16	19.31	0.14	25.67
2	1.50	5.67	1.43	8.00
3	3.73	3.78	5.86	11.16
4	14.62	3.30	13.11	1.92
5	83.98	24.26	60.50	2.21
6	5149.98	3.47	77.80	2.75

Table 2 . Urinary Excretion % for the mean of 6 subjects after the ingestion of 15 sulphadimidine tablets (0.1 gm) 1 ---→ 6.

Time	*Control*	*Sulphadimidine Tables*						*r*	
		1	2	3	4	5	6	*Dist.water*	0.1 N HCl
1	2.12	1.56	1.84	1.82	1.51	1.08	0.45	-0.8182	-0.9342
		(73.58)[x]	(86.79)	(85.85)	(71.23)	50.94)	(21.70)	(-0.8601)	(0.9342)
3	9.03	8.52	7.72	7.35	4.84	4.44	1.55	0.7695	-0.9108
		(94.35)	(85.49)	(81.40)	(53.60)	49.17)	(17.17)	(-0.7903)	(-0.9107)
6	28.11	24.55	24.00	18.15	12.24	13.96	3.85	-0.7348	-0.8394
		(87.34)	(85.38)	(64.57)	(34.54)	(49.66)	(13.70)	(-0.7724)	(-0.8391)
9	42.57	39.02	37.95	30.90	21.45	23.32	6.02	-0.7883	-0.8678
		(91.66)	(89.15	(72.59)	(50.39)	(54.78)	(14.14)	(-0.8159)	(-0.8619)
12	53.41	50.40	48.28	41.57	29.88	30.87	7.94	-0.8222	-0.8871
		(94.36)	(90.40)	(77.83)	(55.94)	(57.80)	(14.87)	(-0.8445)	(-0.8797)
24	80.09	73.64	71.33	62.65	49.13	53.77	11.68	-0.8825	-0.8586
		(91.95)	(89.06)	(78.22)	(61.34)	(67.14	(14.58)	(-0.(106)	(-0.8456)

* ( ) = Physiological Availability % .

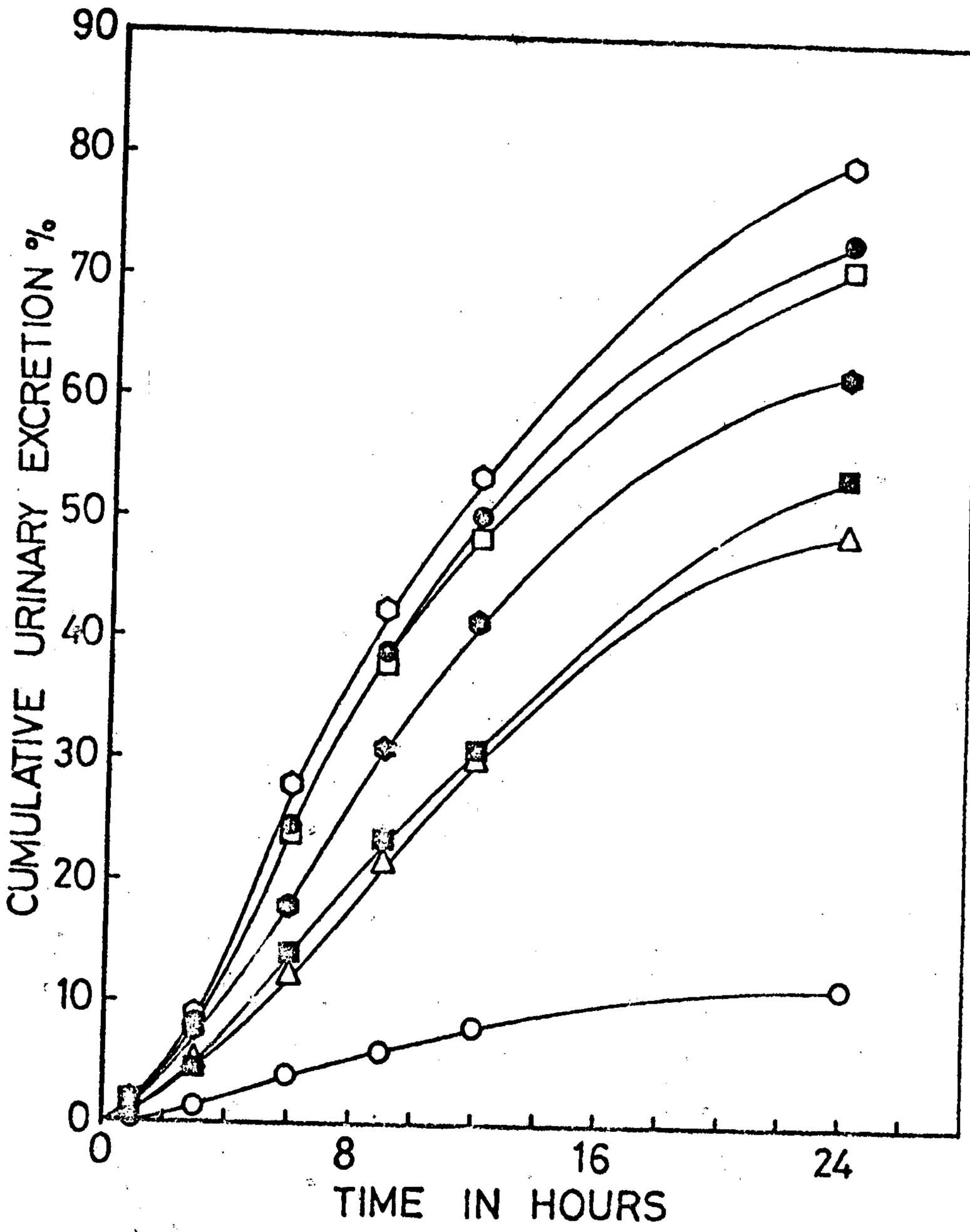

Figure (1) Cumulative Urinary Excretion% (Mean of 6 subjects) after the ingestion of Sulphadimidine Tablets of various disintegration times.

Key: of Disintegration Times, Minuts, B.P (0.1N HCl)
○,zero ; ●,0.14 ; □,1.43 ; ⬢,5.86 ; △,13.11 ; ■,60.50; ○,77.80

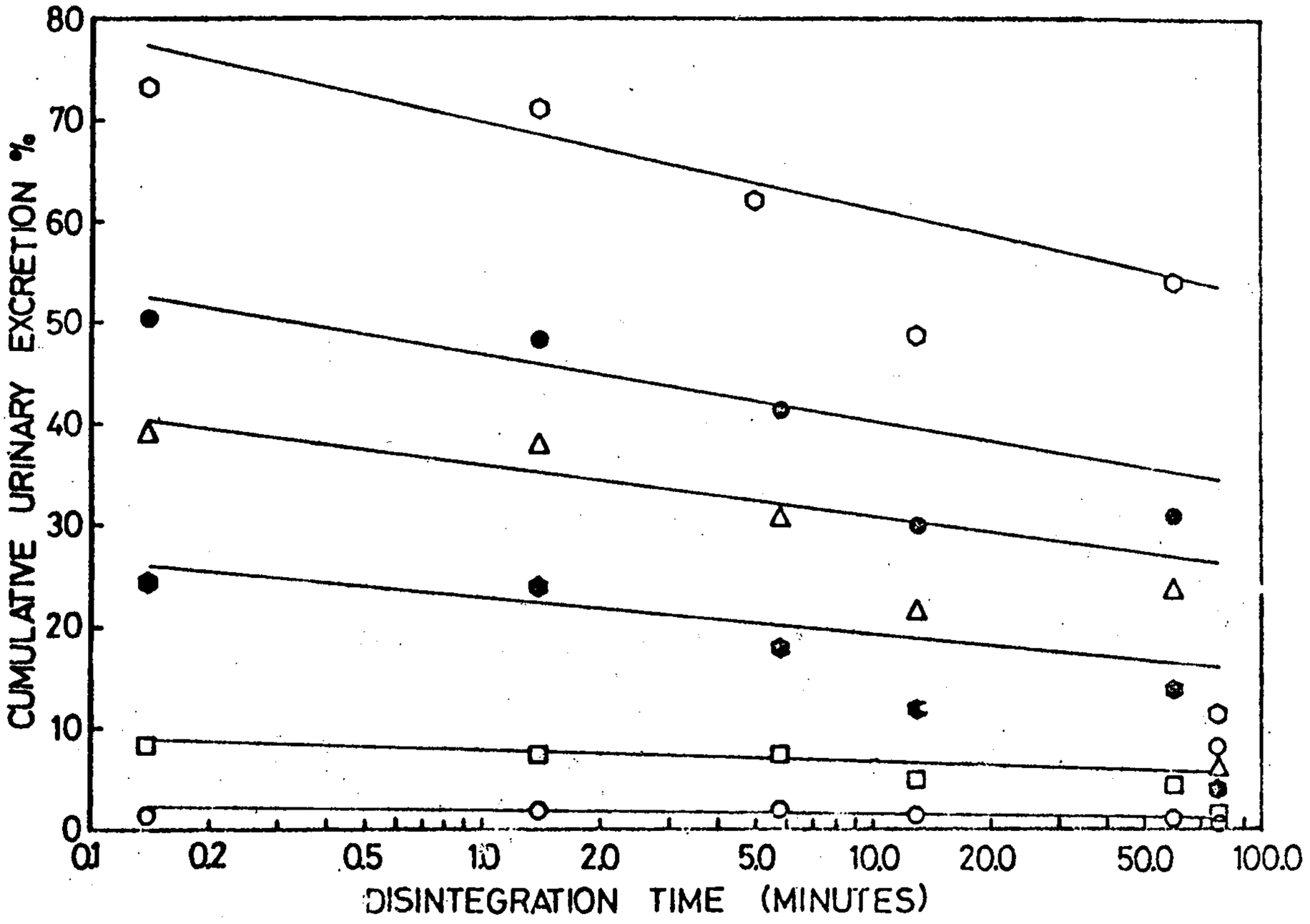

Figure (2) Relationship between disintegration time (B.P., 0.1 N HCl) and cumulative urinary excretion % at various time intervals (Mean of 6 subjects).

Key: for time intervals :

○ 1 hour □ 3 hours ● 6 hours △ 9 hours ◉ 12 hours ○ 24 hours

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دراسة على العلاقة بين تفتت أقراص السلفاديميدين المحضره بطريقة الكبس المباشر وتوافرها الفسيولوجى فى الانسان.

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عادل محمد على

تمت الدراسة على زمن تفتت أقراص السلفاديميدين المحضره بطريقة الكبس المباشر باستخدام السيلوتاب كمواغ لمعرفة درجة توافرها الفسيولوجى فى الانسان وقد أختيرت لهذه الدراسة مجموعات من الاقراص ذات زمن تفتت مختلف. وقد استخدام طريقة الاستخراج فى البول وجد أن هناك علاقة بين زمن التفتت ودرجة الامتصاص فى الانسان لاقراص السلفاديميدين المحضره. كما ثبت أيضا أن الاقراص التى تفتت خلال وقت قصير تعطى أعلى كمية من الامتصاص كما هو واضح من معدل الاستخراج الذى تم حسابه من الكمية المجمعه من السلفاديميدين المستخرجه فى البول.