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EFFECT OF SURFACTANTS TREATED BINDER ON THE PHYSICAL PROPERTIES AND BIOAVAILABILITY OF SULFADIAZINE TABLETS

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The effect of untreated gelatin binder along with surfactant treated gelatin on the physical properties of sulfadiazine tablets were studied. Surfactant treated gelatin was found to lower the d.t., and hardness, but increased friability value. Further, the effect of surfactant treated gelatin incorporated in sulfadiazine tablets, on the dissolution rate was studied and was found to be better than untreated ones. Concentration of 2.5% of surfactant proved to be the most convenient in producing tablets with good physical properties and high dissolution rate. The maximum urinary excretion of sulfadiazine and higher phisiological bioavailability were observed in case of tablets prepared with surfactant treated gelatin.

Concentration of drugs at the site of action is the limiting step in producing its maximum therapeutic response. Parrott et al [1] indicated the importance of dissolution kinetics in determining the drug availability to the body. Subsequently, the dissolution rate does indeed control the rate of build-up of certain drugs in the blood stream[2-4]. The relationship between the disintegration time, dissolution rate and the physiological availability of compressed tablets has

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received a great attention during the last few years. Many factors have been reported to affect the disintegration of tablets[5]. Disintegration time has been reported to be dependent on the binder type and concentration[6,7], or inclusion of surfactants in tablets formulations[8,9]. Disintegration of slightly soluble drugs was found to be highly affected by utilization of surfactants during granulation, than soluble drugs[10]. Surfactants effects were also extended to the tablets mechanical properties[11]. Kedvessy and Musci[12] reported that Tweens 20 and 80 (T 20 & T 80) increase friability, similar was the findings by Aradi[13].

In the present investigation, three surfactants treated gelatin, along with untreated one were used as a binder in an attempt to prepare a tablet with superior physical properties and lower disintegration time. Further, in an attempt to find out the effect of treated gelatin on the drug release, as well as the <u>in-vivo</u> availability. For this purpose, sulfadiazine was chosen as model drug because of its poor solubility (1: 13,000). Tweens 20, 60 and 80 in three concentrations (1.5, 2.5 and 5%) were selected as types of nonionic surfactants, because studies on their oral ingestion revealed them to be relatively inert[14, 15].

EXPERIMENTAL

<u>Materials</u>:

Sulfadiazine, B.P. (ACF, Holland), Tweens 20, 60 and 80 (Prolabo, Paris), Gelatin gepulvert (Merck, Dermstadt), Potato starch(BDH, England), Talc (El-Nasr Chemical and Pharmacetical Co., Cairo, ARE).

Equipment:

Tablet Press, Erweka-Apparatebau, G.M.B.H., E.K.O., West Germany. , Erweka Tablets Hardness Tester, Erweka-Apparatebau, West Germany. , USP Disintegration Apparatus, Erweka-Apparatebau, G.M.B.H., West Germany. , Roche Friabilator, Erweka-Apparatebau, G.M.B.H., West Germany. , USP Dissolution Apparatus, Erweka DT, West Germany., Unicam Sp UV Spectrophotometer.

Methods:

Granulation and Preparation of Tablets:

To prepare the granulating fluids, concentrations of 1.5, 2.5 and 5% w/w of Tween 20, 60 and 80 were added separately to a solution of binder used (gelatin, 10% w/w). 20 mls of the granulating fluid was found to be enough to granulate 100 gm. sulfadiazine powder. All sulfadiazine granules were prepared using wet granulation method[16]. 10% w/w potato starch as disintegrant and 2% w/w talc as lubricant were mixed with the granules in a drum mixer. Tablets were made using single punch Erweka tablets press. The machine was set to produce tablets with average weight 300 mg. The machine settings were kept constant through the compression. Tablets with no surfactants were prepared under the same conditions for comparative study.

Evaluation of the Physical Properties of Prepared Tablets:

The tablets were evaluated for the uniformity of weight (B.P. & USP), uniformity of thickness (micrometer) , hardness (Erweka hardness tester), friability (Roche friabilator) and disintegration time (USP). The results obtained

are presented in Table 1:

In-vitro Study:

The USP XIX-NFXIV dissolution basket was used with 500 ml of 0.1N HCl as dissolution medium and stirring rate of 50 r.p.m. 3 mls samples were taken at several intervals by means of syringe and filtered through millipore filter (Swinnex 0.45 um) and the sulfadiazine concentration was determined using Braton and Marshall[17] method. The percent drug released was calculated on the basis of the total drug content for each tablet. An equivalent quantity of dissolution medium was added to the dissolution vessel immediately after each volume was withdrawn.

In-Vivo Availability Study:

For this study, tablets containing Tween 20, 60 or 80 in concentration of 2.5% w/w were selected on the basis of their good physical and mechanical properties. These were compared with those containing no surfactants.

Twelve healthy male subjects, age between 24-30 years, and weighing between 60-80 Kg were invited for this investigation. All subjects were refrained from any medication during and at least two weeks before the experiments were carried on. Tablets equivalent to 900 mg drug from each batch were given on an empty stomach with a tumbler of water of 250 ml. No food was allowed for at least 3 hours after the ingestion of the tablets. Ample amount of water or fluids were taken frequently during the day. The urine was collected quantitatively at intervals of 1,3,6,9,12 and 24 hrs. or in

between after administration of drug. Control experiments were run for each subject in the same manner as the test , but using 900 mg of drug packed in packet.

The total of acetylated and free sulfadiazine was determined in urine aliquots by allowing acid hydrolysis of the acetylated drug to take place[18]. The total drug in urine was determined colorimetrically using the micromodification technique of Bratton and Marshall[17] method. The cumulative excretion precent and the physiological availability at each time interval were calculated according to Morrison et al[19].

$$\text{Physiological availability } \% = \frac{\% \text{ of dose excreted from the test preparation}}{\% \text{ of dose excreted from the control preparation}}$$

RESULTS AND DISCUSSION

Uniformity of weight and thickness:

All tablets were found to satisfy the B.P. and USP requirements for weight uniformity (Table 1). The coefficient of variation did not exceed 2% . The uniformity of thickness results within each batch were found to be parallel to those of weight.

Mechanical properties:

From Table 1, it is demonstrated that the hardness of the tablets with surfactant treated gelatin was found to be lower (2.25-4.5), than those prepared with plain one (7.25). These findings are in agreement with that obtained by Agrawal

et al[11] working on surfactant treated potato starch as disintegrants. On the other hand, it has been reported that the tensile strength of tablets made from lactose powder coated with spans as nonionic surfactants decreased as the concentration of surfactants increased[20]. It was assumed that the surfactants acted as lubricants or dispersing media, smoothing and softening the surface of the particles. Thus, the surfactants prevent the particles from interlocking with each other. and decrease the strength of the solid bond between them.

As regards the friability, it was revealed that incorporation of surfactant treated gelatin (5%) resulted in too fragile tablets. The friability increased with increase in surfactant concentration. These findings are in accordance with the results of many investigators[11-13].

Disintegration time:

From Table 1, it was demonstrated that the d.t was found to decrease with increase in the concentration of surfactants (1.5-5%). All tablets prepared with the treated gelatin gave lower d.t. It was reported that spraying of the granules before compression into tablets[8], as well as the treatment of drugs with surfactant prior to compression[9], were found to improve tablet disintegration. These results are in agreement with the findings of many investigators[8,9,21,22]. Thus, surfactants are recommended to decrease the hydrophobicity of the drugs[21], because the more hydrophobic the tablets, the greater the d.t.[23]. Aoki and Fukeda[10] claimed that the d.t. of surfactant treated granules of slightly soluble drugs was decreased. This is due to the increase in speed of water penetration as the result of addition of surfactants.

Dissolution rate:

Figures 1-3 represent the in-vitro dissolution profiles of sulfadiazine tablets containing treated and untreated gelatin binder. The tablets prepared with untreated gelatin exhibited a slower drug release, than those containing treated gelatin. The dissolution study revealed that the control tablets were completely dissoluted after 190 min. On the other hand, tablets prepared with surfactants treated gelatin had the highest dissolution rate. Concentration of surfactant less than 1.5% was found to be insufficient to produce a significant increase in disslcution rate. With 1.5% surfactant concentration, the time for 90% drug release from the tablets prepared with T 80 treated gelatin was found to be less than that with other types. The T_{90} for these tablets was found to be 120, 105 and 90 min. for T 20, T 60 and T 80 respectively. The time taken to release 50% of the drug shows a similar pattern(Table 1) which is a further evidence that T 80 in such concentration is recommended to be incorporated in the gelatin binder for tablets production. Concentration of 2.5 and 5% of surfactants exhibited a higher rate of dissolution, but with no significant difference could be obtained between the three types of surfactants used (T 20. T 60 and T 80). All of them exhilit approximately the same effect on dissolution rate. T_{50} was found to be 7.5 min. for tablets prepared with T 80 (5%) treated gelatin, while it was found to be 63 min. in control tablets. Enhancing the drug release from the tested tablets could be explained on the fact that, the presence of surfacntants resulted in fast disintegration and to lower mechanical strength of the tablets. In other words, the penetration of the dissolution medium into the tablets as a result of incorporation of the surfactants may destroy the cohesive bonds between the particles, so the surface area subjected to the dissolution

medium is increased, consequently a high dissolution rate was expected. The decrease in dissolution rate obtained in the case of control tablets is probably due to the lower swelling and breakage of the gelatin binder bridges between the particles and is also due to the increase in mechanical strength of the tablets especially in the absence of surfactants. Also , the absence of surfactants produced tablets possessing more hydrophobic characters than the treated ones. These may act by slowing the rate at which the invading dissolution medium reaches the surface of the powder particles. From table 1, it is clear that the disintegration results confirm those of dissolution rate values.

Bioavailability study:

The urinary excretion rate of sulpha drugs was claimed to reflect directly blood level concentrations. The 24 hours urinary excretion results (Table 2) indicated that tablets with surfactant untreated gelatin were readily excreted in urine in the amount of 34.51%. During the first 3 hours, a delay in sulfadiazine excretion was observed in tablets prepared with treated or untreated gelatin. This delay in excretion was also reported in case of sulfthiazole[24]. T 20 shows the lowest drug excretion in urine after 24 hours (44.6%), while T 60 and T 80 show a higher amount (51.8%). On the other hand, sulfadiazine powder used as control shows an amount of 69.4% in urine. Physiological availability was found to be higher after 24 hours in case of sulfadiazine tablets with surfactants treated geltin (64.3, 74.6 and 74.6% in case of T 20, T 60 and T 80 respectively) than those prepared without surfactants (49.7%). The role of surfactants in enhancing drug absorption was explained by Blanpin[25] as that the surfactants can affect the integrity of biologic membranes.

Table 1: Physical properties of the sulfadiazine tablets prepared with and without surfactants

Type preparation	Weight, g.* Mean	C.V.%	Thickness, mm** Mean	C.V.%	Hardness, Kg* Mean	C.V.%	Fraibility %**	Disintegration*** time, min.	Dissolution** Rate, $T_{50\%}$	min. $T_{90\%}$
Control	0.31922	0.91	5.19	0.35	7.25	13.6	0.185	6.25	63	190
Tween 20										
1.5%	0.32145	0.87	5.18	0.44	3.95	10.41	0.383	4.56	18	120
2.5%	0.32323	0.65	5.23	0.32	3.25	9.39	0.620	4.25	9	60
5.0%	0.31950	0.66	5.20	0.29	2.25	12.49	0.719	3.50	9	43.5
Tween 60										
1.5%	0.32325	0.87	5.21	0.32	4.00	7.63	0.356	4.25	17	105
2.5%	0.32250	0.96	5.25	0.36	3.65	4.90	0.608	4.33	10	65
5.0%	0.32008	0.53	5.22	0.34	2.65	6.79	0.720	3.33	9	36
Tween 80										
1.5%	0.31789	0.69	5.15	0.42	4.30	6.61	0.372	4.30	11.5	90
2.5%	0.32138	0.56	5.23	0.17	3.75	5.01	0.542	3.75	9	65
5.0%	0.32408	0.56	5.24	0.44	3.10	5.23	0.590	3.50	7.5	37.5

* Average of 20 readings
** Average of 5 readings
*** Average of 12 readings

Table 2: Mean cumulative precent excretion of sulfadiazine and percentage physiological availability

Time	*Control*	*No Surfactants*		*2.5% T 20*		*2.5% T 60*		*2.5% T 80*	
		A	*B*	*A*	*B*	*A*	*B*	*A*	*B*
1	2.48	0.37	0.533	0.38	0.548	0.40	0.576	0.41	0.591
3	14.01	2.62	3.780	3.53	5.087	2.50	3.603	4.17	6.010
6	29.80	10.51	15.146	13.03	18.777	12.10	17.437	15.53	22.381
9	43.85	15.51	22.352	19.47	28.059	23.24	33.492	24.39	35.149
12	52.65	23.86	34.385	27.26	39.285	27.32	39.372	32.54	46.894
24	69.39	34.51	49.733	44.64	64.332	51.81	74.665	51.83	74.694

A= Mean Cumulative Percent.

B= Physiological Availability Percent.

Effect of surfactants treated binder on the physical properties and bioavailability of sulfadiazine tablets

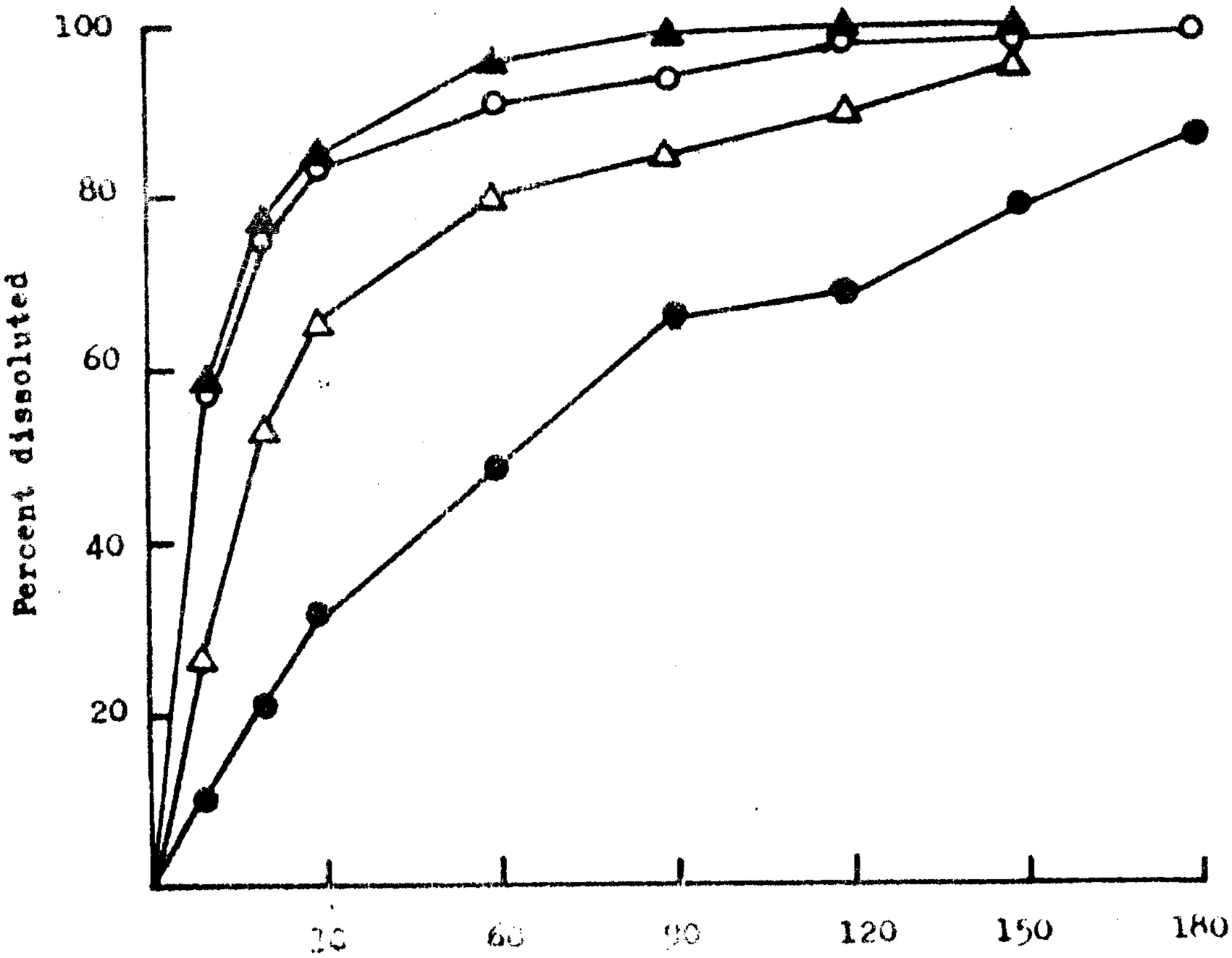

Fig. 1: Effect of Tween 20 on the dissolution profiles of Sulfadiazine Tablets. Concentration of T 20 were as follows. ● Blank; Δ 1.5%; O 2.5%; ▲ 5%

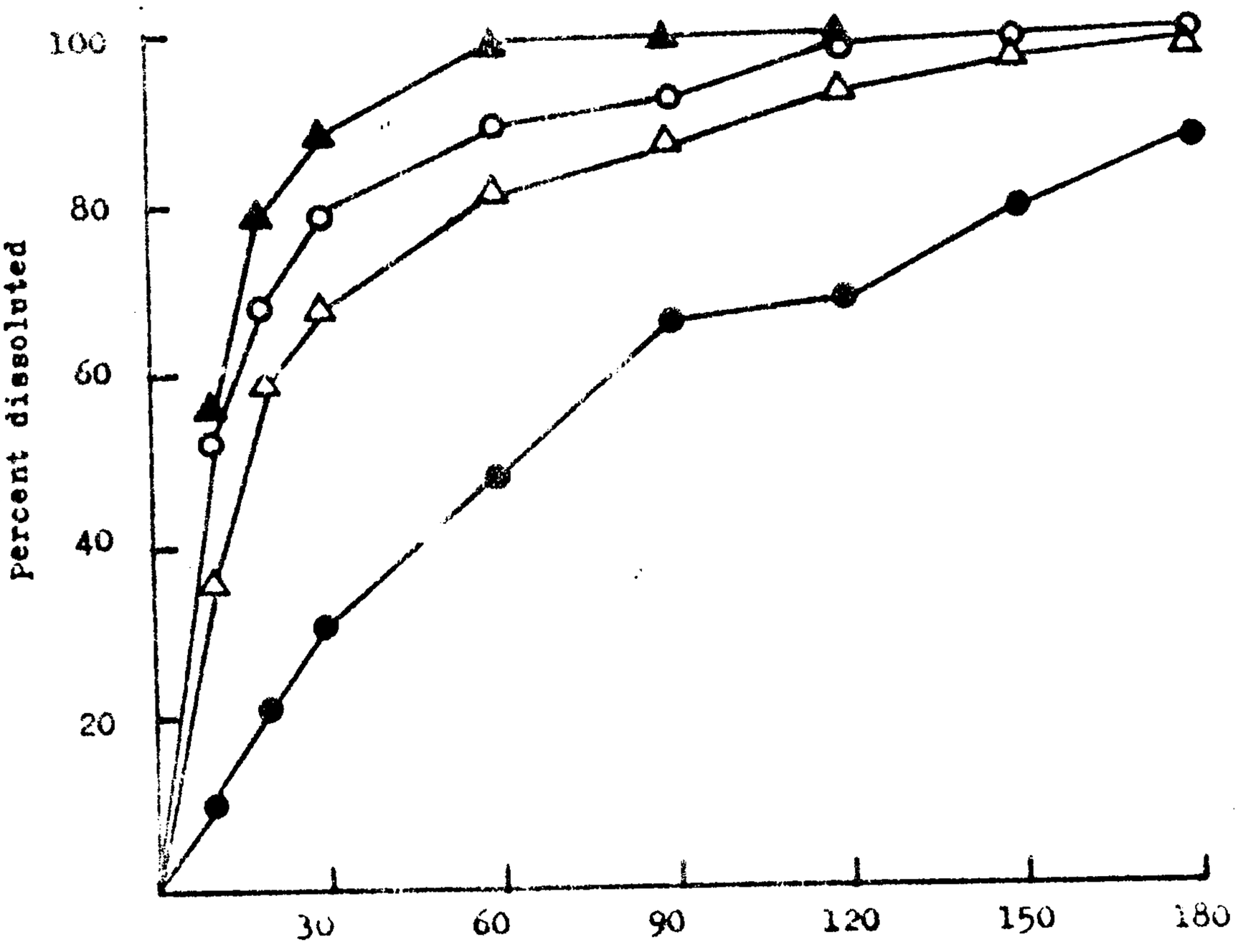

Fig. 2: Effect of Tween 60 on the dissolution profiles of sulfadiazine Tablets. Concentration of T 60 were as follows; ● Blank; Δ 1.5%; ○ 2.5%; ▲ 5%.

Effect of surfactants treated binder on the physical properties and bioavailability of sulfadiazine tablets

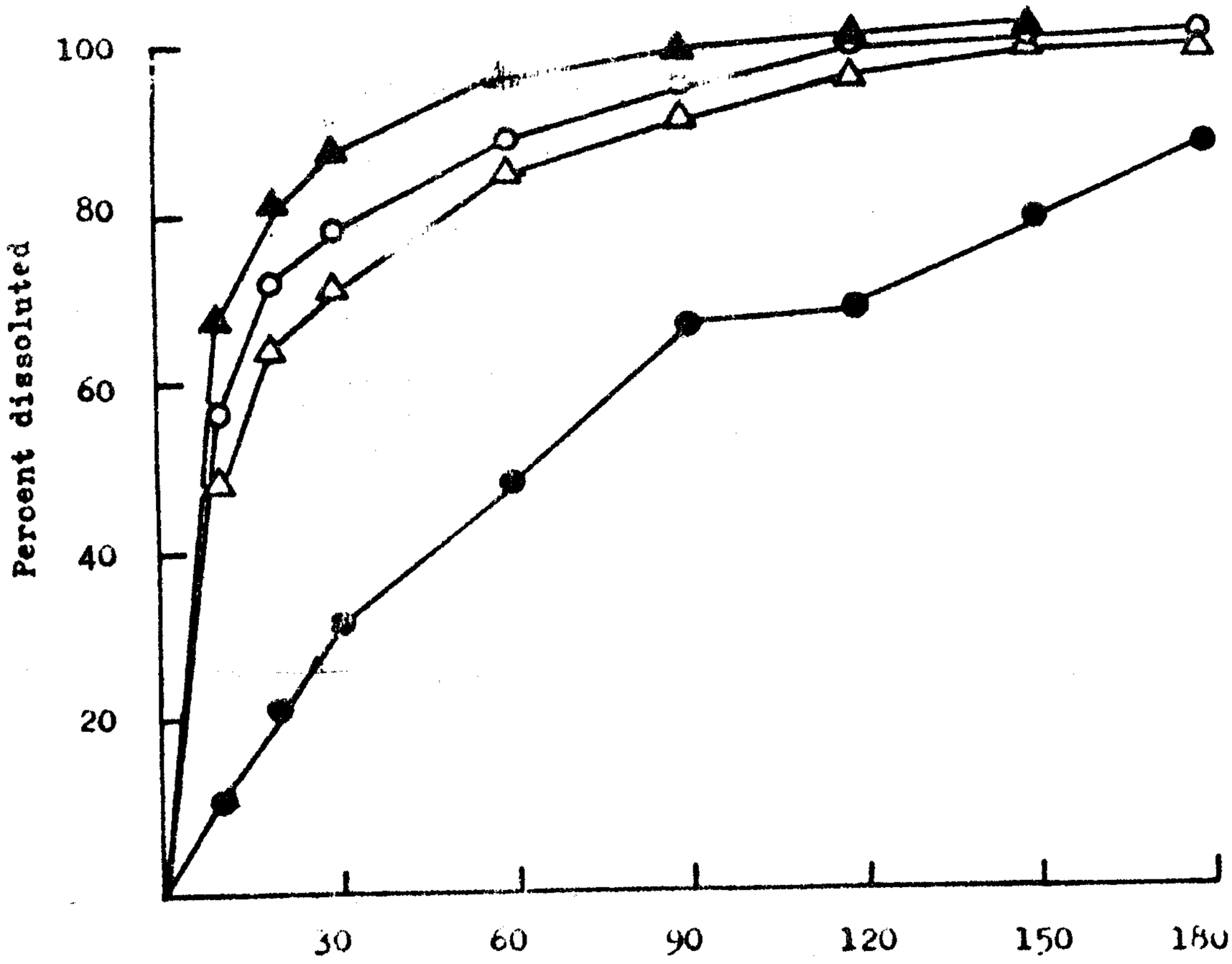

Fig. 3: Effect of Tween 80 on the dissoultion profiles of sulfadiazine Tablets. Concentration of T 80 were as follows; ● Blank; Δ 1.5%;2.5%; ▲ 5%

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تاثير أحدى الروابط والمعاملة ببعض المواد ذات النشاط السطحى الغير متـــــــائنة عـــلى الخواص الطبيعية والاتاحة الحيوية لاقـــــراص الســـــــــلفاديازين

حسن الصباغ ـ محمدحامد الشابورى ـ احمدطلعت نوح ـعبد الحوادحلمـــــى .

كليـــــة الصيدلة ـ جامعة المنصـــورة

يتنـــاول هذا البحث تحضيـــر اقراص السلفاديازين بطريقة التحبيب الرطب وذلك باســـــــتخدام أحـــدى المواد الرابطة (محلول الجيلاتين ١٠٪) والتى تحتـــوى على تركيـــزات مختلفـــة من بعـــض المـــواد ذات النشاط السطحـــــى والغيـــــــر متاينـــة (تـــوين ٢٠ ، توين ٦٠ ، توين ٨٠)٠

ولقـــــد تمت دراسة الخـــواص الطبيعيـــة ومعدل الانطـــلاق لعقـــــــار الســـــلفاديازين وكـــذا معـــدل الاتـــاحة الحيويـــة له ولقد تبين مـــــن نتـــائج البحث ان تركيـــز ٥٪ من التويـــن ينتـــج اسهلة التفتت وذات خـواص طبيعيـــة رديئـــة . ولقـــد تبين من البحث ان تركيز ٥ر٢٪ من التويـــن ٢٠ ، ٦٠ ، ٨٠ يعطى أقـــراصا جيـــدة من حيث الخواص الطبيعيـــة وقصر زمـــــن الـــذوبـــان ومعـــــدل الانطـــلاق كذلك الاتاحة الحيويـــة للاقراص

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