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DISSOLUTION BEHAVIOUR OF TOLAZAMIDE IN THE PRESENCE OF CERTAIN NON-IONIC SURFACTANTS.

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ABSTRACT

The dissolution rate of tolazamide, an oral hypoglycemic drug, was studied in distilled water as well as solutions of polysorbates and myrjs at 30°C using the beaker method. The surfactant concentration was increased from 0.001 to 0.5% W/V in order to study the effect of the surfactant concentration on the dissolution rate of tolazamide. The relative area under the curve, from 0 - 60 minutes (R.A.U.C.$_{0-60}$) was used as a parameter to compare the effect of different surfactants, used at the same concentration (0.5% W/V), on the dissolution rate of tolazamide. It was found that the amount of the drug dissolved was significantly dependent on the concentration of each surfactant used as well as the type of the surfactant. The mechanism of the increase in the dissolution rate was also discussed.

INTRODUCTION

Drugs administered orally in solid dosage forms must be dissolved before absorption. The dissolution rate of slightly water soluble medicals is considered to be the most important factor in the absorption process. Therefore, a knowledge of the dissolution rate is helpful in the pharmaceutical formulations.

The effect of surfactants on the aqueous solubility of slightly water soluble drugs has been investigated[1-6]. In a homologous series of surfactants, the cationic agents have been found to be more effective than the anionics, while the nonionics are considered to be the most effective ones. Within certain limits, the solubilization of the polar solubilizates was found to be favored by more hydrophilic surfactants. On the contrary, lipophilic surfactants have higher solubilizing capacities for those non-polar solubilizates. The solubilizing efficiency for certain solubilizates has been found to vary directly with the ethylene oxide chain length[7].

The present work is an attempt to investigate the effect of certain non-ionic surfactant solutions (polysorbates and Myrjs) on the dissolution rate behaviour of an oral hypoglycemic agent, tolazamide. Such surfactants, in the correct concentration, may potentially be formulated in soft gelatin capsule or compressed tablet dosage forms of tolazamide so as to improve its bioavailability.

EXPERIMNTAL

Materials:

The non-ionic surfactants* chosen for the present study were: Polyoxyethylene (20) sorbitan monolaurate (polysorbate 20), polyoxyethylene (20) sorbitan monopalmitate (poysorbate 40), polyoxyethylene (20) sorbitan monostearate (polysorbate 60), polyoxyethylene (20) sorbitan monooleate (polysorbate 80), polyoxyethylene (40) stearate (myrj 52), polyoxyethylene (50) stearate (myrj 53) and polyoxyethylene (100) stearate (myrj 59). The oral hydroglycemic agent, tolazamide, was kindly supplied by Upjohn Co. (USA).

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* Atlas Chemical Company, Del. USA.

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Determination of the Dissolution Rate:

The dissolution rate was determined by the beaker method[8]. The dissolution assembly consisted of a 500 ml. Pyrex beaker immersed in a thermostatically controlled water bath adjusted at 30°C and a glass stirrer attached to an electrical stirring motor giving the stirrer a constant speed of rotation of 50 r.p.m. A series of aqueous solution containing various concentrations (0.001 %, 0.01 %, 0.1 % and 0.5 % W/V) of the selected surfactants were used as dissolution media. 250 ml. of the corresponding dissolution medium were placed into the beaker and allowed to equilibrate at 30°C. The stirrer was immersed in the middle of the dissolution medium and 0.5 gm tolazamide powder, having a particle size range of 90 - 100 µm, was sprinkled over the surface of the dissolution medium. At certain time intervals, 2 ml samples were withdrawn with pipettes provided with a short plastic tubings filled with a piece of cotton and immediately replaced with equal volume of the dissolution medium. The withdrawn samples were assayed spectrophotometrically at 262 nm[9] after appropriate dilution with distilled water. A Shimadzu double beam spectrophotometer (Japan) was used for this purpose. It has been found that the presence of the surfactant molecules did not interfer in the spectrophotometric assay of the drug in the dilution range used.

RESULTS AND DISCUSSION

Dissolution of a slightly water soluble drug is consisered to be a consecutive process, which consists of:

a) Surface interaction leading to the formation of a new solid-liquid interface.
b) solvation of the solid at the interface .
c) transfer of the solvated solid into the bulk of the dissolution medium. This process could be summarized as follows:

Solid $\xrightarrow{\text{surface interaction}}$ Solvent ... Solid $\xrightarrow{\text{solvation}}$

Solvated Solid at the interface $\xrightarrow{\text{mass transfer}}$ Solution.

The effect of concentrations and types of some selected polysorbates and myrjs on the extent of the dissolution rate of tolazamide has been investigated at 30°C. The concentration of each surfactant used covered the range from below to above its respective CMC.

The dissolution profiles of tolazamide are illustrated in figures 1-7 . The cumulative amount (in mole/L) dissolved was plotted versus the dissolving time (in minutes).

From these figures it could be observed that during the first minute , the dissolution rate of tolazamide in the presence of the different concentrations of the selected surfactants was significantly increased as compared with control. The increase in the dissolution rate, when the concentration of the surfactant was below its CMC (0.001 % W/V), may be due to the formation of local association concecntration (LAC) of the surfactant molecules or due to the adsorption of some surfactant molecules on the surface of the solid particles resulting in improving the wettability of the solid by the liquid and accordingly the effective surface area was actually increased resulting in an increase in the dissolution rate. When the concentration of the surfactant used was beyond its CMC (i.e 0.01 % W/V or more) , the concentration of tolazamide dissolved was markedly increased. Also, from these figures it could be observed that as the concentration of the surfactant was increased, the amount of tolazamide dissolved was correspondingly increased. This increase in the disslution rate may be explained on the basis that tolazamide molecules were incorporated within the micellar core. The amount of

the drug dissolved in the surfactant solution is dependent on the apparent partition coefficient of the drug between the micellar and the intermicellar phases. As the concentration of the surfactant is increased above its respective CMC, the apparent volume of the micellar phase will be increased resulting in an increase in the amount of the drug incorporated inside the micellar core.

From the data obtained, it could be considered that there was a difference among the dissolution rates of tolazamide in the presence of the selected surfactants. This difference in the dissolution behaviour should give rise to a difference in the drug bioavailability. From the figures 1-7, it was observed that the amount of tolazamide dissolved was increased as the dissolving time was increased until it reached a maximum at about 40 minutes, after which further increase in time produced no change in the amount of the drug dissolved. The relative area under the curve from 0-60 minutes ($R.A.U.C._{0-60}$)* was used as a parameter to compare the solubilizing efficiency of the selected surfactants, when they were used at 0.5 % W/V. The trapezoidal method was used to calculate the area under the curve.
From Table 1, the surfactants could be ranked in a decreasing order, according to their solubilizing effect as follows: polysorbate 20 > polysorbate 80 > polysorbate 40 > polysorbate 60 > myrj 59 > myrj 53 > myrj 52.

The solubilizing effect of polysorbates, having the same polyoxyethylene chain length and differ mainly in the hydrocarbon chain, was greater than myrjs which are characterized by having the same lipophilic group and very in the hydrophilic portion. With myrjs the amount of tolazamide

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* R.A.U.C. = A.U.C. in presence of surfactant / A.U.C. of the control

dissolved was markedly increased as the number of ethylene oxide units was also increased. This observation revealed that most of tolazamide molecules tend to be concentrated in the palisade layer of the micelle. As regard to the effect of polysorbates on the dissolution rate of tolazamide it was found that the most enhancing effect was attained in the presence of polysorbate 20. This could be explained on the assumption that the molar ratio between the hydrophilic portion and the lipophilic one is much greater in polysorbate 20 than in the other tested polysorbates. Finally, it appears that the micellar size and structure formed with different surfactants have played an important role in the observed enhanced dissolution rate.

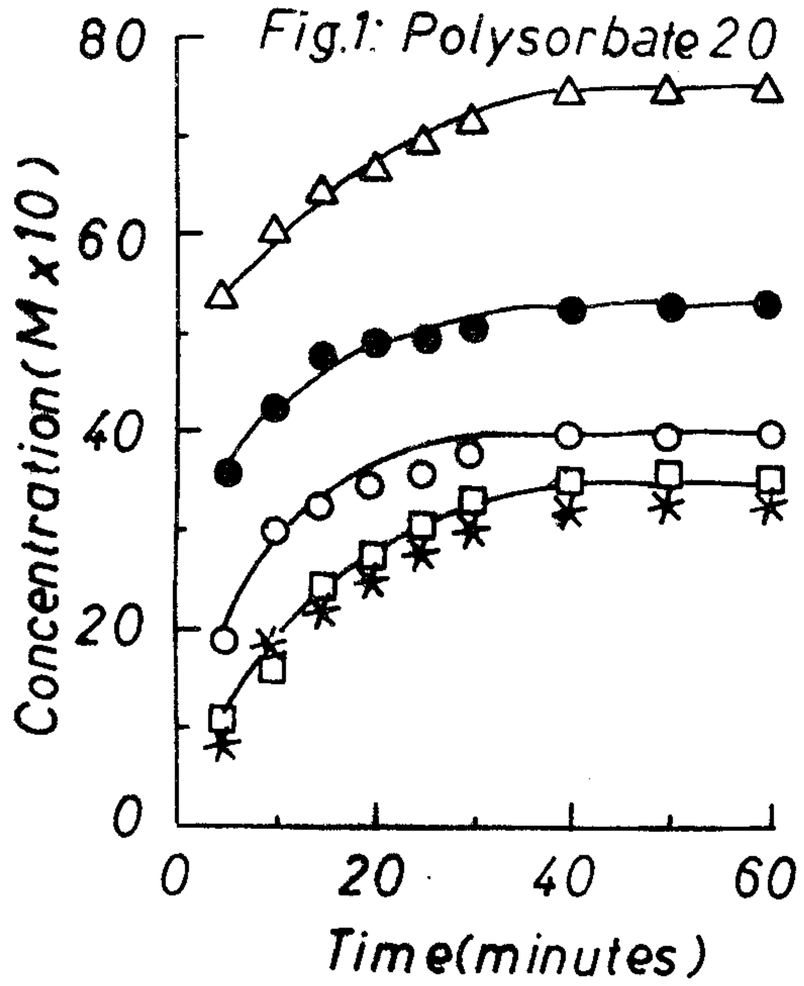
Dissolution Behaviour of Tolazamide in the Presence of Certain Non-Ionic Surfactants.

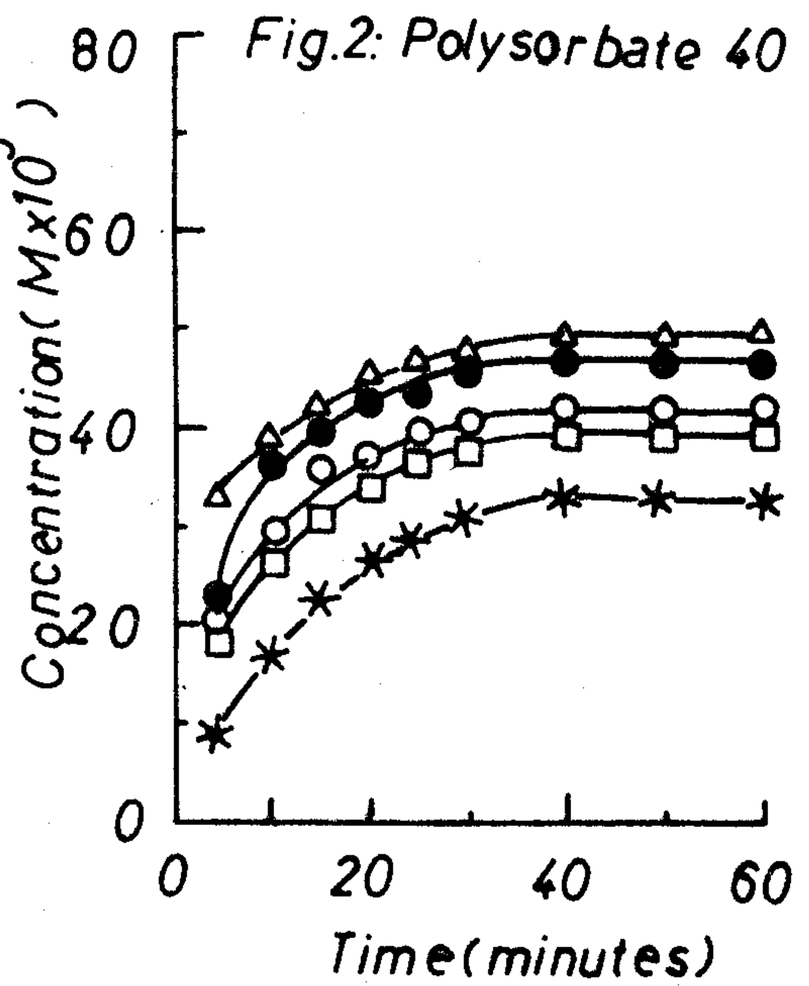
Table 1. A.U.C. and R.A.U.C. for the Dissolution Behaviour of Tolazamide in 0.5 % W/V of Different Non-Ionic Surfactants at 30°C and 50 r.p.m.

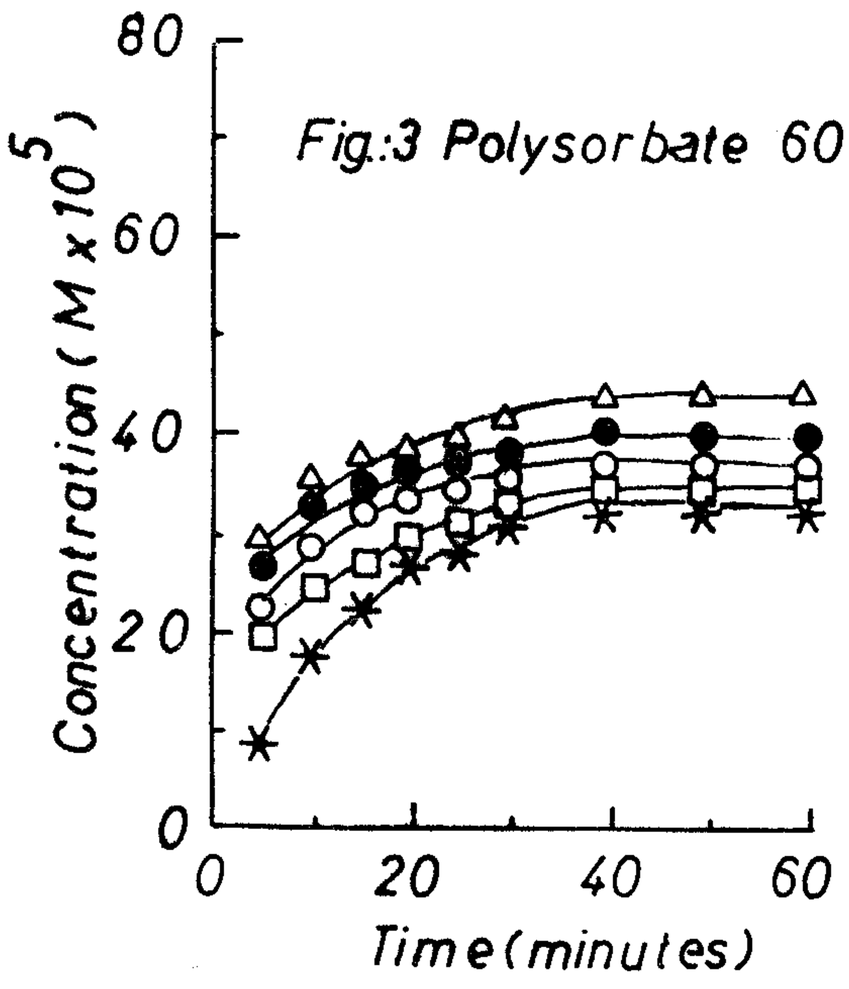
Surfactant	A. U. C.	R. A. U. C.
Polysorbate 20	4005	2.563
Polysorbate 80	2895	1.853
Polysorbate 40	2660	1.702
Polysorbate 60	2325	1.488
Myrj 59	2280	1.459
Myrj 53	2245	1.437
Myrj 52	2160	1.382

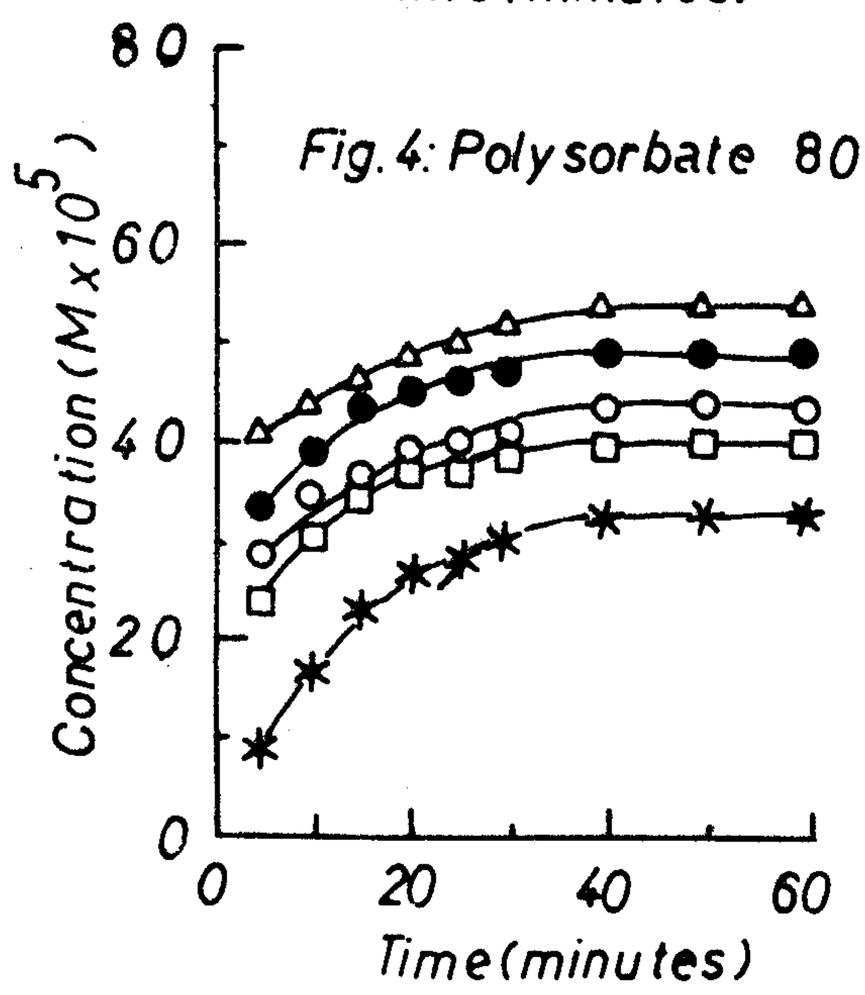
N.B. The A.U.C. for the control = 1562.5

Dissolution Behaviour of Tolazamide in the Presence of Certain Non-Ionic Sureactants.



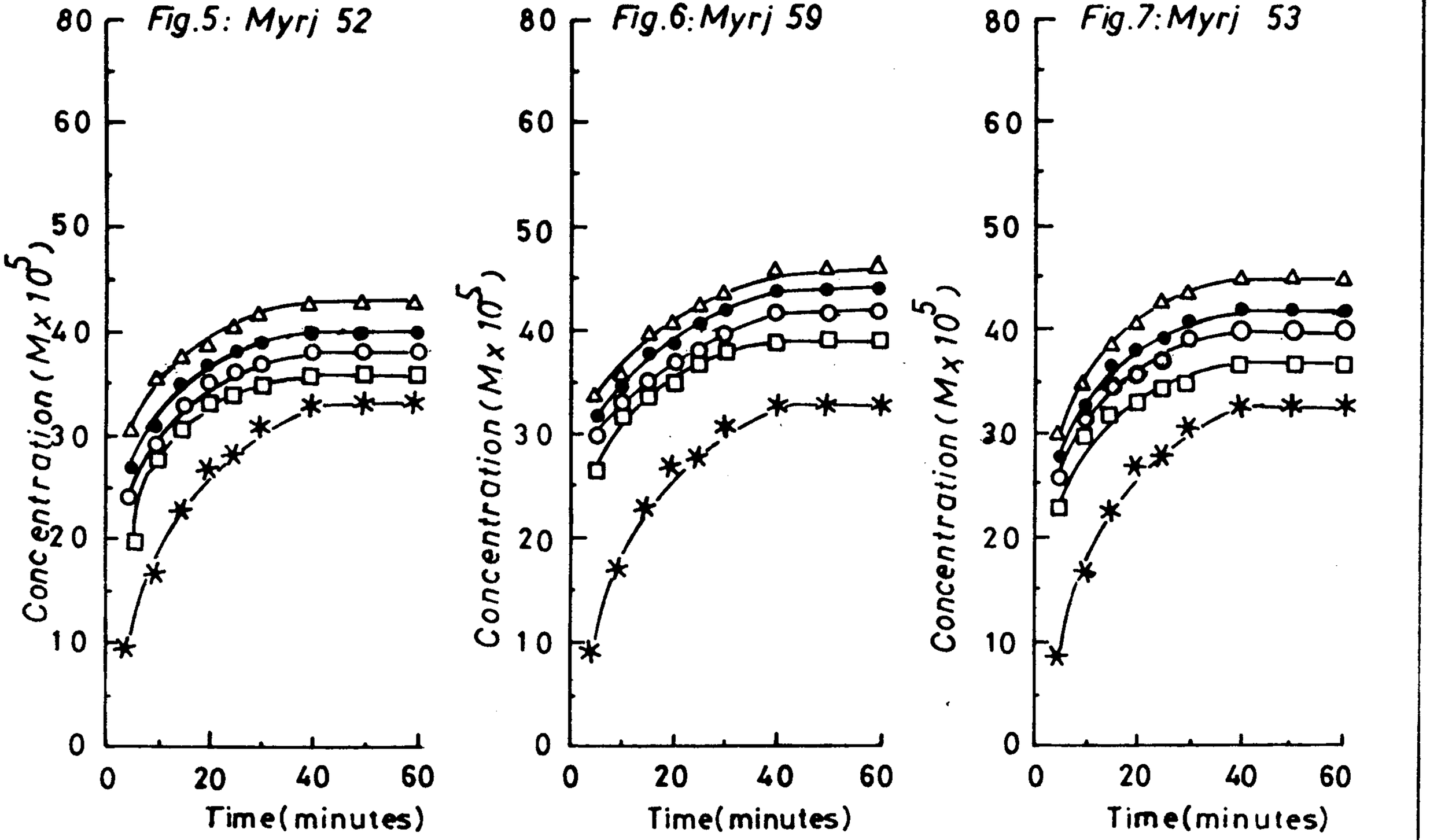






FIGURES (1-4). DISSOLUTION BEHAVIOUR OF TOLAZAMIDE IN PRESENCE OF CERTAIN POLYSORBATES.

key: ✱—✱ Control; □—□ 0.001%; ○—○ 0.01%; ●—● 0.1%; △—△ 0.5%



FIGURES (5–7) DISSOLUTION BEHAVIOUR OF TOLAZAMIDE IN PRESENCE OF CERTAIN MYRJS.

Key: as in figs. 1–4.

REFERENCES

1) A.L. Thakkar and N.A. Hall, J. Pharm. sci., 58, 68 (1969).

2) M. Gibaldi, S. Feldman and N.D. Weiner, Chem. Pharm. Bull., 18, 715 (1970).

3) S. Miyazaki, H. Inoue, T. Yamahira and T. Nadia, ibid., 27, 2468 (1979).

4) J.H. Collett, R. Withington and L. Koo, J. Pharm. Pharmac., 27, 46 (1975).

5) H. Krasowska, Pharm. Ind., 40, 1381 (1978).

6) T. Arnarson and P.H. Elworthy, J. Pharm. Pharmac., 33, 141 (1981).

7) A.G. Mitchell and L.S.C. Wan, J. Pharm. Sci., 53, 1467 (1964).

8) G. Levy and B.A. Hayes, New Engl. J. Med., 262, 1053 (1960).

9) United States Pharmacopeia, XIX, p. 510 (1975).

سلوك اذابة تولازاميد فى وجود بعض منشطات السطح الغـــــير متـأينة

سيد اسماعيل محمد ـ على عبد الظاهـــــــر عبد الرحمن

قسم الصيدلانيات قسم الصيدلة الصناعية

كلـــية الصيدلة ـ جامعة اســـيوط

تم دراسة معدل اذابة التولازاميد فى الماء المقطر وكذا فى المحاليل المائية لبعض انواع البولى سوربات والميرج وذلك عند عند درجة حرارة ٣٠ م باستخدام طريقة الكأس . ولدراسة تأثير تركيزات منشطات السطح على معدل الاذابة للتولازاميد فلقد زيدت هذه التركيزات تدريجيا من ٠٠١رو/ ح الـــى ان اصبحت ٥ر. / و/ح .

ولقد تمت المقارنة بين معدلات الاذابة لهذه المنشطات السطحية بحســـاب المساحـــة التى تقطع تحت منحنى الاذابة لكل منشط سطحى عند تركيز ٥ر/ و/ح بطريقة شبه المنحرفات فى الفترة الزمنية من الوقت الصغرى وحتى ٦٠ دقيقـــــة ولقد وجد ان معدل الاذابة يعتمد اعتمادا كليا على تركيز المنشط السطحـــى المستخدم وكذا ايضا على نوعه . ومن الدراسة العملية يمكن ترتيب المنشطات السطحية بناء على الزيادة فى معدل الاذابة على النحو التالى : ـ

بولـــى سوربات ٢٠ > بولى سوربات ٨٠ > بولـــى سوربات ٤٠ >

بولـــى سوربات ٦٠ > مـــــــــيرج ٥٩ > مـــــــــيرج ٥٣ > مـــــــيرج ٥٢ .

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