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INTRACTION OF 1,4-BENZODIAZEPINES WITH CERTAIN MACROMOLECULES: I- EFFECT OF NON-IONIC SURFACTANTS ON THE DISSOLUTION RATE OF TEMAZEPAM

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ABSTRACT

A recycling and automatic recording system was adopted for studying the dissolution of Temazepam via dispersed particulate and intrensic dissolution methods. The study involves the effect of concentrations below and above CMC of polysorbates and Myris on the solubility and dissolution rate of Temazepam at 37°C. These Surfactants in low concentrations (below their CMC) caused no change in Temazepam solubility referred to its water solubility.

T50% and RDR (relative dissolution rate) for Temazepam powder were calculated from the dissolution profiles. The presence of the studied surfactants in the dissolution medium caused an increase in the dissolution rate of the drug as demonstrated by a decrease in the T50% and the increase of the RDR. An explanation for these results is offered.

The static disc method of dissolution was adopted in order to investigate the effect of the studied surfactants on the dissolution rate of Temazepam compressed discs. Plots of the amount of Temazepam dissolved, in the presence of the studied surfactants, as a function of time, were linear for the intrensic dissolution of Temazepam discs.

Correlation studies between the used surfactant cencentrations and dissolution rate as well as solubility parameters of Temazepam were carried out and analyzed. It is suygested that the dissolution of Temazepam in the presence of the colloidal micellar surfactants is a diffusion controlled process and is related more to the diffusion layer mechanism of dissolution.

INTRODUCTION

The use of surfactants as emulsifying agents, solubilizers, suspension stabilizers and as wetting agents in formulations intended for adminstration to human subjects or to animals can lead to significant changes in biological activity of the active agents in the formulations. A drug is seldom administered as such but as a complex formulation. Surfactant molecules incorporated into the formulation can exert their multifarious effects in several ways. e.g., by influencing the deaggregation and dissolution rates of solid dosage forms, by controlling the rate of precipitation of drugs administered in solution form, by increasing membrane permeability and affecting membrane integrity[1]. Study of the interaction between bile salts and indomethacin and phenylbutazone showed that the enhancement of the dissolution of indomethacin in the presrnce of bile salts was mainly due to micellar solubilization. On the other hand, the enhanced dissolution of phenylbutazone may be due to the melting effect and the increasing effective surface area of the powder[2]. Parrott and sharma[3] have shown that surfactants increase the dissolution rate of benzoic acid,while Wurster & Seitz[4] and Levy & Gumtow[5] also observedan increased dissolution rate in the presence of sodium lauryl sulphate. The dissolution rate of griseofulvin is increased in the presence of surfactants[6,7].

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In the present study, Temazepam, a 1,4-benzodiazepine derivative, utilized in clinical practice as rapidly acting hypnotic drug[8] was chosen for studying the influence of low concentrations of non-ionic surfactants on its measured dissolution rate.

EXPERIMENTAL

Materials:

Temazepam, (Fabrica Italiana, Laboratorio controllo Alte Monteechio Italy) I.R. and M.P. measured agreed with reference determination.

Macromolecules:

Polyoxyethylene (20) sorbitan monopalmitate, polyoxyethylene (20) sorbitan monooleate (polysorbates 40 and 80 respectively), (sigma chemical company, U.S.A.). Polyoxyethylene (40) stearate, poly oxyethylene (100) stearate (Myrjs 52 and 59 respectively), (Atlas chemical Industries Ltd., England).

Apparatus:

- Shaking water bath (Grant Instruments, Cambridge Ltd., England).
- SE 292 Digital ultraviolet spectrophotometer, (Instrum = NTS, Cambridge, England).
- Multipen recorder (Rikadenki Mitsni Electronirs Ltd., England).
- Dissolution apparatus (Erweka-Apparatebou, G.m.b.H., Germany).

Procedures:

I. Solubility Determinations:

Excess of Temazepam was shaken with 10 ml of different concentrations of surfactant solutions for 24 hours in a constant temperature water bath

at 37 ± 0.2 C. 2 ml of the suspension were filtered and 1 ml of the filtrate was diluted to 50 ml with distilled water. The concentration of the drug was determined by measuring the U.V. absorption at 232nm. Equilibration beyond 24 hours did not increase the solubility.

II. Determination of the dissolution rates:

A recycling and automatic recording system was used for all the dissolution studies, i.e., the solution in the dissolution vessel was automatically pumped (by a peristaltic pump) through 10 mm path length quartz flow cell of the spectrophotometer and then back to the dissolution vessel. The absorbance of Temazepam at 232 nm was recorded to give a continuous plot of absorbance versus time.

The dissolution apparatus used was similar to that described by USP/NF Method 2, with slight modifications. During dissolution, the dissolution medium was agitated at a rate of 100 r.p.m. under sink conditions by keeping the concentration of the drug less than 5-10% saturated solubility, as maintained during the experiment. In each case, during dissolution an appropriate concentration of the surfactant was circulated at first (as a blank) to avoid interference. All samples were run at least in dublicate.

(A) Dispersed Particulate Method:

Temazepam (8 mg, 45-200 μ) was sprinkled over the surface of the dissolution medium (900 ml degased solutions of polysorbates or Myrjs). The experiment was completed for 30 minutes as above.

(B) Intrinsic Dissolution Method:

Discs (10 mm diameter, 1.5 mm thickness) were prepared by compressing (25 kg/cm^2) Temazepam (165 mg, 45- 200 μ) using a special die. The disc surface was cleaned with a jet of air before use. Discs were not removed from the dies but the entire unit was fitted flush into the base

of the dissolution medium so that the upper face of the disc was exposed to the dissolution medium. The dissolution process was measured as before.

RESULTS AND DISCUSSION

Table 1 shows the saturation solubilities of Temazepam in water and in different concentrations of polysorbates and Myrijs below and above their reported CMC values at 37[9]. With regards to the obtained results, it can be concluded that polysorbstes and Myrjs in low concentrations (below their CMC) cause no change in Temazepam solubility, This is mostly because surface active molecules are molecularly dispersed, and compounds with low water solubility, such as Temazepam, do not dissolve to a greater extent than they would in water. However, at concentrations of surfactants above their CMC, the solubility of Temazepam was increased which may be attributed to micellar solubilization of the drug.

$T_{50\%}$ and RDR (relative dissolution rate) for Temazepam powder, as calculated from the dissolution profiles of the amount of Temazepam dissolved against time are shown in Table 1. It is evident that presence of surfactants in the dissolution medium causes an increase in the dissolution rate of Temazapam as demonstrated by a decrease in the $T_{50\%}$ and the increase of R.D.R. The increase in the dissolution rate of the drug in the presence of low concentrations of polysorbates and Myrjs, used below CMC, may be attributed to a lowered interfacial tension which improved the wetting of the powder surface and the effective surface area consequently increased[10]. A higher concentration (above CMC) of polysorbates and Myrjs causes also an increase in the dissolution

rate which may be due to micellar solubilization, wetting effect and increasing the effective surface area of the dispersed powder. This behavior agrees with the diffusion layer theory of dissolution[11].

The static disc method was adopted in order to investigate the effect of surfactants on the dissolution rate of Temazepam in a more quatitative manner, which may help predicting the mechanism of dissolution. Plots of the amounts of Temazepam dissolved as a function of time were linear for intrinsic dissolution method studies of Temazepam in different concentrations of Myrj 52, Fig.1. Increasing the surfactant concentrations increased the dissolution of the drug. The apparent zero dissolution rate constants (K) obtained are listed in Table 2. According to the Noyes-Whitney relationship,[12] under sink conditions and with constant surface area, dissolution rate (d.r.) may be expressed by the following equation:

$$d.r = \frac{dc}{dt} = K\ (C_s - C) \qquad ...(a)$$

which shows that the rate of change of the concentration of a solute, C, is related to its saturation solubility, C_s (assuming constant surface area). Under sink condition, $C_s >> C$, and equation (a) can be reduced to:

$$d.r. = K\ C_s \qquad ...(b)$$

where K is the dissolution rate constant.

In non micellar systems: $K = \frac{D}{h}$

where D is the solute molecule diffusion coefficient and h is the effective diffusion layer thickness . Keeping the surface area of the disc constant and assuming that both D and h remain invarient if the drug is dissolved in a medium containing colloidal solubilizer, then it may be deduced from equation (b) that:

$$R = \frac{C^*_c}{C_s} \qquad ...(c)$$

where R is the ratio of dissolution rate in surfactant solution to that in pure solvent and C_s^* is the drug solubility in surfactant solutions. Using the solubility data obtained in the present work the theoretic dissolution ratioS employing equation (C) were determined and drawn,Fig. (2).

This Figure also shows the experimental ratio of dissolution rate constants. The latter plot is non-linearly related to dissolution rate, becoming progressively less with an increase in the surfactant concentration. Similar phenomena have been demonstrated by Higuchi[13], who found that the ratio of dissolution rate of benzocain in polysorbate 80 solution, to that without the surfactant,was substantially lower than that predicted by the Noyes-Whitney theory. These results have been supported by several workers[3,14,15].

This Finding might indicate that the Noyes-Whitney theory fails to predict dissolution in systems contaning solubilizers. This effect may be due to an increase in the viscosity of the dissolution medium[16], or due to dependence of the dissolution rate on the diffusion coefficient of the diffusing species, and not on their solubilities; as micellar solbuilized drugs would have a lower diffusion coefficient than the free drugs. According to Higuchi[13], the effect of interacting colloids on dissolution rates may be used for differentiation of the dissolution mechanism. From the present results, this may indicate that the dissolution is a diffusion-controlled process and is related more to diffusion layer mechanism of dissolution.

Table 1- Dissolution Half Lives ($T_{50\%}$)*, R.D.R.* and Solubility of Temazepam in the Dissolution Media Containing Various Concentrations of Surfactants at 37° using Dispersed Dissolution Method.

Dissolution Media	Surfactnat concentration % w/v	Solubility µg/ml of Temazepam	$T_{50\%}$(MIN)	R. D. R. at Minutes	
				10	20
Water	0.000	144	15.6	1	1
Polysorbate 40	0.0005	143	5.2	6.86	3.34
	0.1	149	3.6	9.72	4.19
Polysorbate 80	0.0005	145	6.3	5.95	3.17
	0.01	150.9	4.3	8.55	3.87
Myrj 59	0.005	146	4.4	7.48	3.50
	0.05	148	3.2	8.60	3.79
Myrj 52	0.005	144.1	4.0	7.65	3.62
	0.05	151	3.0	9.63	4.12
	0.1	160	---	---	---
	0.5	250	---	---	---
	1.00	360	---	---	---

* $T_{50\%}$: time required for 50% of the drug to be dissolved
* R.D.R. (Relative Dissolution Rate): ratio of the amount of the drug dissolved in the non-ionic surfactant medium divided by the amount dissolved in water at the same time interval.

Table 2 – Dissolution Rate Constants*, their Ratio and Solubilities of Temazepam in Myrj 52 Solution

Surfactant Concentration (% w/v)	Dissolution rate constants (mg min^{-1}) x 10^3	Ratio of solubility	Ratio of dissolution rate constant
0.000	12.47	----	----
0.005	14.08	1.001	1.129
0.1	17.14	1.111	1.345
0.5	19.30	1.736	1.548
1.0	23.10	2.500	1.853

* Related to static disc method for studying dissolution.

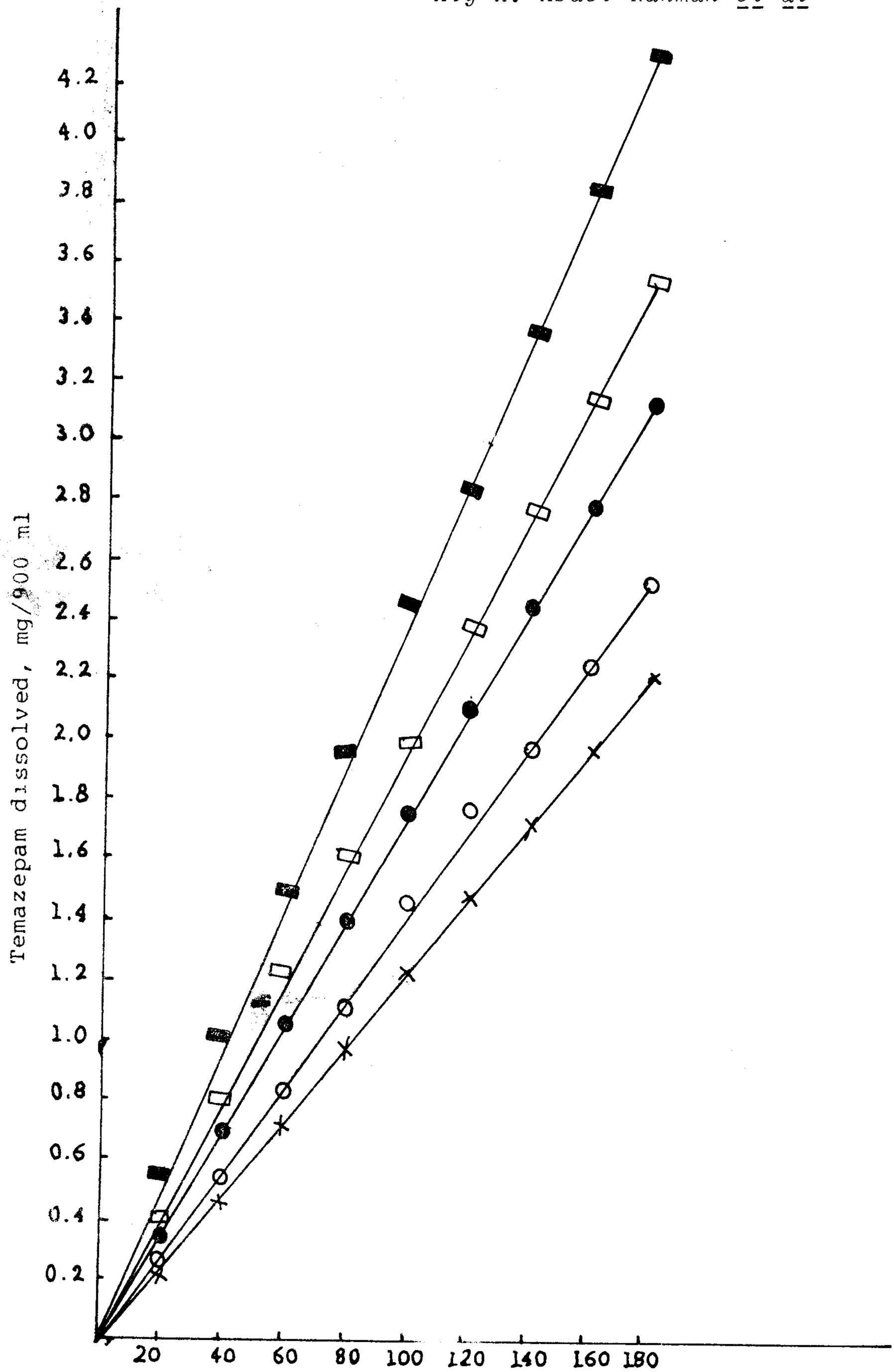

Fig. 1 : Dissolution of Temazepam in water containing various concentrations of Myrj 52 at 37° using Static Disc Method.

Key : x, 0.00% w/v Myrj 52 ; ○, 0.005% w/v Myrj 52; ●, 0.1% w/v Myrj 52; □, 0.5% w/v Myrj 52 ; ■, 1.0% w/v Myrj 52

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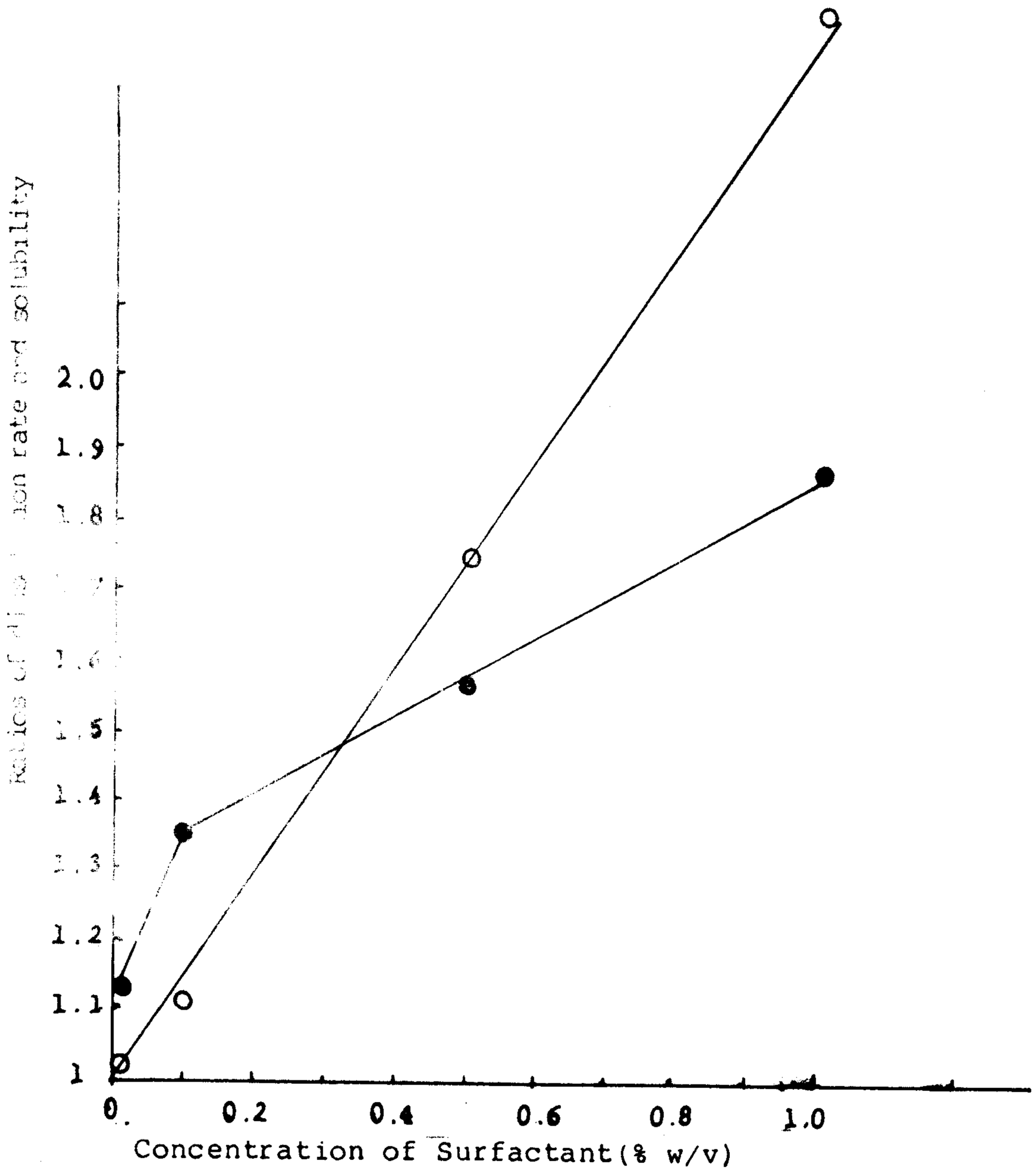

Fig.2: Ratio of Dissolution Rates and Solubilities of Temazepam in Myrj 52 solution to those in distilled water using Static Disc Method.

Key: O , ratio of solubility; ● , ratio of dissolution rate constant.

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تفاعلات مجموعة ١و٤ ـ بنزوديازبين مع بعض الجزئيات الكبيرة
(١) تاثير منشطات السطح غير المتأينة على معدل اتاحة التيمازيبام

براين ارثر مللى ـ احمد السيد ابو طالب ـ على عبد الظاهر ـ سيد محمد احمد

كلية الصيدلة ـ جامعة براد فورد انجلترا ـ قسم الصيدلة الصناعية ـ كلية الصيدلة

جامعة اسيوط

تم تصميم نظام اوتوماتيكى دائرى تسجيلى لدراسة اتاحة التيمازيبام ـ ولقد تم استخدام طريقة انتشار الجزئيات والاتاحة من سطح ثابت لدراسة تأثير تركيزات من منشطات السطح غير المتأينة قبل وبعد التركيزات الحرجة لتكوين الشباك لكل من البوليسوربات والميرج على الاذابة ومعدل الاتاحة لعقار التيمازبيام عند درجة ٣٧ مئوية ٠

ولقد وجد ان البوليسوربات والميرج قليلة التركيز الحرج لتكوين الشباك ليس لها تأثير على اذابة التيمازبيام بالنسبة الى ذوبانه فى الماء ٠

وقد حسب معدل الاتاحة والاتاحة النسبية لمسحوق التيمازبيام من الاشكال البيانية للاتاحة ولقد وجد ان وجود منشطات السطح غير المتأينة فوق وتحت التركيز الحرج لتكوين الشباك يزيد عن معدل اتاحة التيمازبيام وذلك لتأثيرها على تذويب العقار ٠

ولقد اتبعت الاتاحة من سطح ثابت لدراسة تأثير منشطات السطح غير المتأينة كميا على معدل الاتاحة ٠ كما وجد ان معدل الاتاحة مع تركيز منشطات السطح غير المتأينة يمثل علاقة غير خطية وذلك نظرا لزيادة لزوجة وسط الاتاحة ٠

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