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A NEW APPROACH FOR ENHANCING THE DISSOLUTION RATE OF PHENACETIN

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ABSTRACT

Numerous attempts are conducted so as to develop a rapid dissolution rate for those poorly water-soluble drugs. A new approach for enhancing the intrinsic dissolution rate of phenacetin is ascribed. This technique is based on the concept of the recrystallization of phencetin from different surfactants concentrations. The observed enhancing effect in the dissolution rate of phenacetin, using this technique, may be due to wetting and/or deaggregation effect. The dissolution rate study was investigated in 0.1 N HCl at 37°C and 50 r.p.m. The experimental study showed that the dissolution rate, during the first few minutes, is markedly affected by this technique. The relative area under the curve from 0 to 30 minutes ($R.A.U.C._{0-30}$) was used as a parameter to compare the different dissolution rates of the drug after being recrystallized from 1% w/v of each surfactant solution.

The extent, in the dissolution rate enhancing effect, was found to range from 2.66 to 3.25 times of that of the control. This technique is valuable as a preformulation phase of phenacetin in solid dosage forms.

INTRODUCTION

Different techniques are commonly recognized so as to speed up the dissolution rate of some poorly water-soluble and/or water-insoluble durgs. The most widely used techniques are : complexation (1-4), adsorption onto a water insoluble compound (5), salt formation (6), solid dispersion (7-11), coprecipitate using an inert water-insoluble carrier (12-15) and the use of different water soluble surfactants (16-22).

When a drug is formulated in a solid dosage form and intended to be taken orally, the drug must be dissolved in gastric fluid before it reaches the circulatory system. It well recognized that the dissolution rate of those slightly water soluble drugs is the rate limiting step in their biological availability when they are administered orally as a solid dosage form. The relationship between the dissolution rate and the biological availability has been discussed by Wagner (23). Therefore, a knowledge of the dissolution rate of poorly water soluble drugs is usually servicable for the solid drug formulation techniques.

The water soluble surface-active agents, at concentrations above their critical micelle concentration values (CMC's), are widely used to prepare aqueous solutions of those slightly water-soluble drugs. There is a considerable evidence which suggests that, the pharmacological activity of a micellar solubilized drug is, generally, a function of its concentration in the aqueous phase, whereas, those drug molecules inside the micellar cores being regarded as inactive reserve of the drug (24,25).

The present work was undertaken with the aim of the enhancing the dissolution rate of phenacetin. The technique employed involved the recrystallization of the drug in the presence of different concentrations, above CMC's, of some selected non-ionic surfactants.

EXPERIMENTAL

Materials :

Phenacetin (B.D.H. England), polysorbates 20,40,60 and 80 (Atlas chemical industries Co., USA), hydrochloric acid (Prolabo), myrjs 52, 53 and 59 (Atlas chemical industries Co., USA), dimethylformamide (B.D.H.England), brijs 35 and 58 (Atlas chemical industries Co., USA). All the previously mentioned chemicals were used without further purification.

Recrystallization of Phenacetin :

Stock aqueous solutions (5% w/v) of the tested surfactants were prepared. By appropriate dilutions 1 ,

2 and 3 % w/v aqueous surfactants solutions were prepared. An accurately weighed 2 gm. phenacetin were dissolved in about 3 ml. dimethyformamide at a suitable temperature and the resultant clear solution was poured into 25 ml. of each surfactant solution, previously cooled at about 7°C. The formed crystals were collected immediately by filtration and dried in a desiccator for about 24 hours. The powder was pulverised, sieved and the fraction of the powder having a particle size 100-90 μm was used for the dissolution rate study. The dissolution rate of the pure drug having the same particle size and without recrystallization was also studied.

Dissolution Rate Studies :

250 ml. of 0.1 N HCl were placed in the dissolution cell*. The temperature of the dissolution medium was monitored until stablized at 37°C. The stirring rate was adjusted at 50 r.p.m. and accurately weighed 0.5 gm. of the drug powdered sample was sprinkled onto the surface of the dissolution medium . One ml. aliquot samples were withdrawn using 1 ml. pipette fitted with a small polyethylene tube containing a small piece of cotton to exclude the water-insoluble fine particles of the drug. The withdrawn samples were analyzed spectrophotometrically for its phenacetin content at 245 nm,after appropriate dilutions with distilled water.

* ERWEKA DT-06

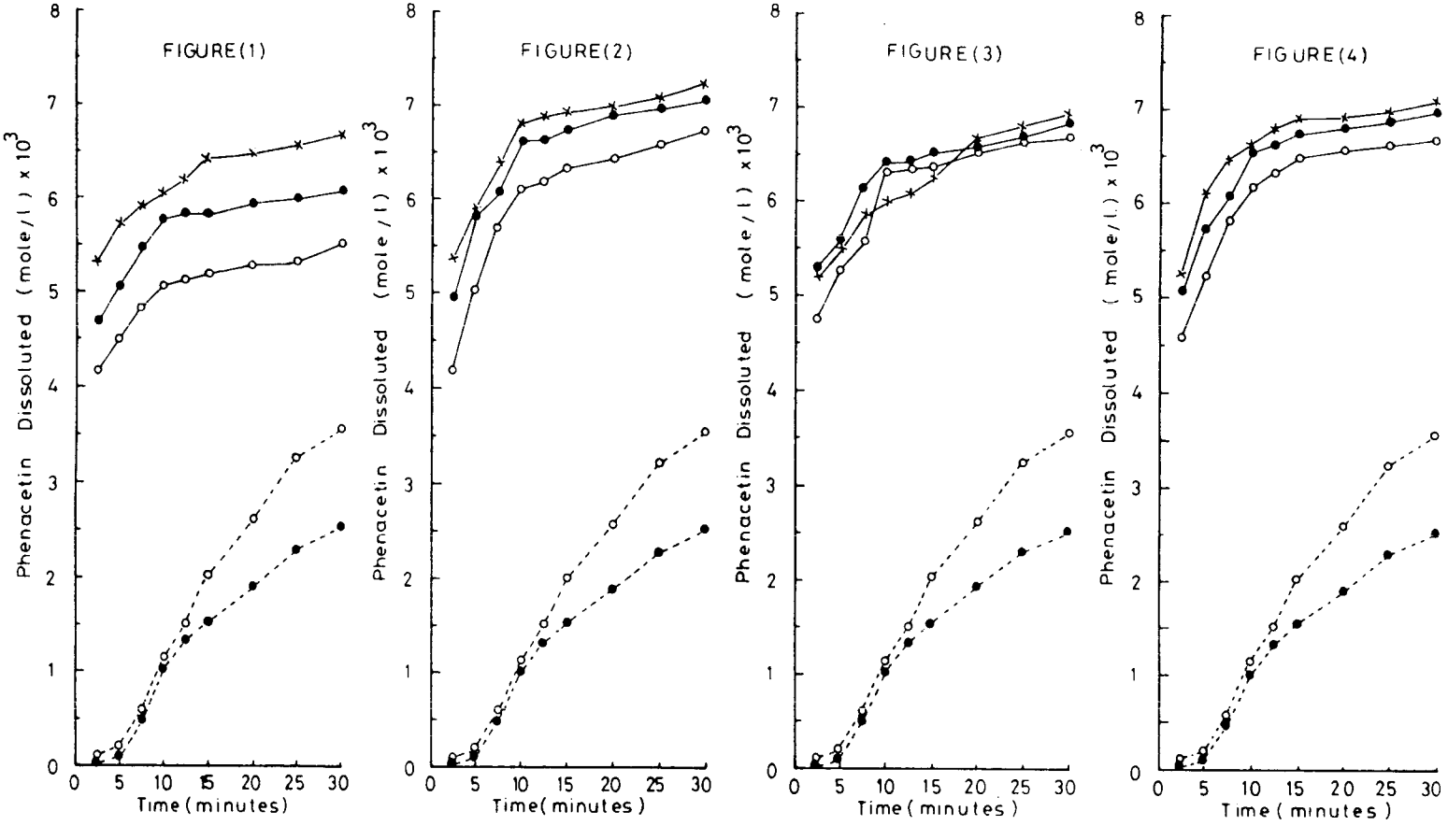
The volume of the dissolution medium was kept constant, during the experimental study, by replacing 1 ml. of 0.1 N HCl to the dissolution medium immediately after each withdrawing.

RESULTS AND DISCUSSION

When a slightly water-soluble drug is immersed in an aqueous dissolution medium, it is basically subjected to three consequetive processes, which are generally responsible for its transfer from a solid state into the bulk of the dissolution medium. These three processes could be summarized as follows : (a) formation of a solid-liquid interface, (b) solvation of the solid at the interface, and (c) transfer of the dissolved solid from the solid-liquid interface into the bulk of the dissolution medium.

The results of the dissolution rate studies, expressed in terms of mole/l. as a function of time are ascribed in in figures 1-9. The figures clearly indicate that there is a significant increase in the dissolution rate of the drug within the first few minutes (15 minutes).

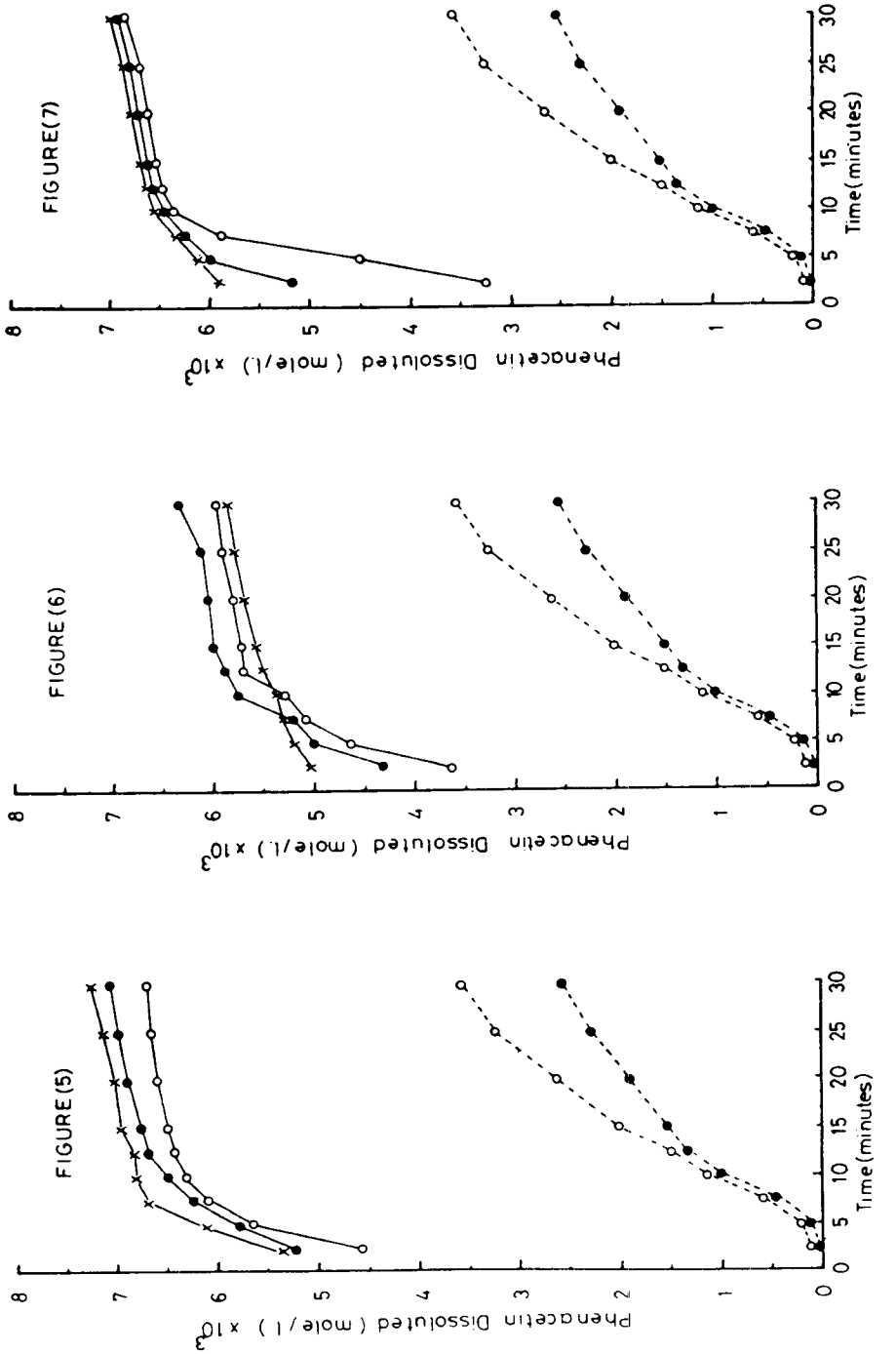
The observed enhancing effect, in the extent of the dissolution rate of phenacetin, after being recrystalized from the surfactants aqueous solutions could be explained through one of the following postulations : (a) the degree of wettability of the drug is markedly increased after crystallization from the surfactants



FIGURES (1–4)

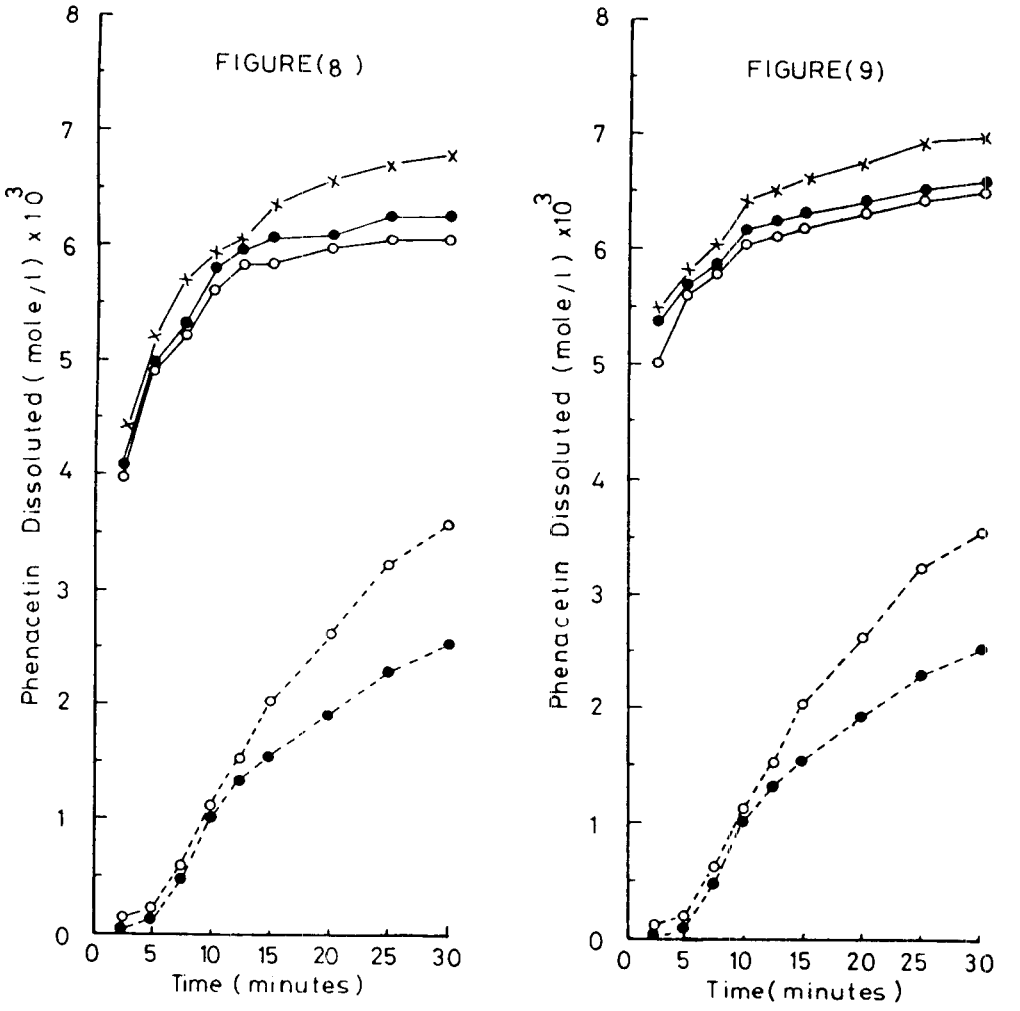
Dssolution Profile of Phenacetin after being Treated with Different Concentratations (% w/v) of Tween 20 (Fig 1), Tween 40 (Fig 2), Tween 60 (Fig 3) and Tween 80 (Fig 4).

key: ●--- Untreated, o--- Control, o— 1% Surfactant, ●— 2% Surfactant and ×— 3% Surfactant



FIGURES (5–7)

Dissolution Profile of Phenacetin after being Treated with Different Concentrations (% w/v) of Myrj 52 (Fig.5), Myrj 53 (Fig.6) and Myrj 59 (Fig.7). key; as figures 1-4



FIGURES(8&9)

Dissolution Profile of Phenacetin after being Treated with Different Concentrations (%w/v) of Brij 35 (Fig 8) and Brij58 (Fig 9) Key; as figures 1–4.

solutions which may be attributed to the adsorption of some surfactant molecules onto the hydrophobic surface of phenacetin crystals. The wetting process which, consists of replacing the solid-air interface with the solid-liquid interface, increased the degree of penetration of the dissolution medium into the drug particles, Accordingly, the rate of formation of a solid-liquid interface is increased and subsequently, the transfer rate of the drug molecules into the bulk of the dissolution medium is increased. (d) deaggregation effect which results in an increase in the exposed solid surface area due to the break up of the secondary particles into the primary ones. The increase in the dissolution rate of aspirin in the presence of some surfactants has been ascribed to either wetting and/or deaggregation effect (26)

It was observed that (27) the in-vitro dissolution rates of sulfathiazole, prednisone and chloramphenicol were markedly enahnced after being crystallized in aqueous surfactant solutions . Also, it was found that (28) the dissolution rate of chlorthalidone crystals was enhanced after crystallization in the presence of some non-ionic surfactants at different concentrations.

It is clearly obvious, from Figs.1-9, that the dissolution rates of phenacetin are, frequently, dependent on both the type and the concentration of the surfactant used in the recrystallization process. The relative area under the curve (R.A.U.C.), table 1, was used as a para-

TABLE 1

Area Under the Curve (A.U.C.) and Relative Area Under the Curve (R.A.U.C.) for the Dissolution Rate of Phenacetin after being Treated with 1% w/v Surfactants Solutions.

Surfactant	A.U.C. x 10^5	R.A.U.C.
Tween 20	14638	2.66
Tween 40	17420	3.16
Tween 60	17768	3.23
Tween 80	17825	3.24
Myrj 52	17898	3.25
Myrj 53	15598	2.83
Myrj 59	17451	3.17
Brij 35	16177	2.94
Brij 58	17517	3.18

N.B. 1) A.U.C. Corresponding to the control = 5507.5

2) A.U.C. for the untreated phenacetin = 4127.5

meter so as to compare the different dissolution rates of phenacetin after being recrystallized from 1% w/v of each surfactant solution. From this table it is obviously observed that most of the surfactatns used in the recrystallization process, have a pronounced enhancing effect towards the dissolution rates. The difference

between the extents of the dissolution rates, ranging from 2.66 - 3.25 folds of that of the control, is not significant. This observation substntiates that the mechanism through which the dissolution rate is enhanced is not only due to the drug-surfactant interactions but also may be due to wetting and/or deaggregation effects.

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