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SURFACTANT SOLUTIONS AS MEDIA FOR DISSOLUTION TESTING OF A POORLY WATER-SOLUBLE DRUG

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ABSTRACT

The solubility of a poorly water soluble drug, 4-(4-biphenylyl)-butanol (I) was dramatically enhanced in the presence of anionic, cationic and non-ionic surfactants. Since I has no bioavailability problems on oral dosing of capsules, physiological surfactants may be involved in the solubilization of I *in vivo*. Thus, surfactant solutions were selected as the most relevant media for dissolution testing of capsules of I. The intrinsic dissolution of I was examined in water, sodium dodecyl sulfate (SDS), and polyoxyethylene lauryl ether (POE lauryl ether) solutions, and

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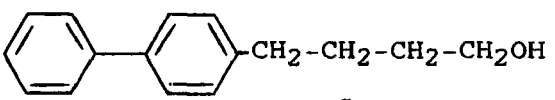
increases were observed. Capsule dissolution in SDS solutions was not very successful; possible reasons are discussed. POE lauryl ether was selected as the surfactant of choice. The intrinsic dissolution rates were not a linear function of concentration of POE lauryl ether in the medium. Reasons for these observations are discussed. Dissolution of capsules was examined in various concentrations of the surfactant and an optimum concentration selected.

INTRODUCTION

4-(4-Biphenylyl)-butanol (I)[1] is a new synthetic non-steroidal anti-inflammatory agent with marked antiphlogistic activity but weak antipyretic and analgesic activities. The aqueous solubility of I is 0.006 mg/ml at 26° and 0.010 mg/ml at 37° and is independent of pH. The octanol/water partition coefficient is also independent of pH and is large (> 2000). Thus, dissolution could be the rate-limiting process in the absorption of I from a solid dosage form. Since the therapeutic dose of the drug is expected to be fairly large (> 100mg/day), it was suspected that the poor aqueous solubility would result in dissolution and bioavailability problems on oral dosing. However, bioavailability and pharmacokinetic studies in dogs indicate that I is almost completely absorbed when given orally in capsules when compared to intravenous administration; doses were similar to those expected in humans[2].



I

The presence of surfactants in intestinal fluid is well documented(1,2) and their presence in gastric fluid has been proposed(3). These surfactants are capable of solubilizing poorly water soluble compounds, thereby increasing the dissolution rate. Thus, if dissolution is the rate limiting process in absorption from solid dosage forms, the presence of physiological surfactants may improve bioavailability; this might account for the absence of bioavailability problems with I.

Various approaches have been suggested for designing dissolution tests for poorly water soluble drugs. These include the use of large volumes of dissolution medium, mixed organic-aqueous solvents (USP XX), two-phase dissolution media with an upper organic layer(4), and the inclusion of surfactants(5-8). The last approach might be most physiologically relevant for the dissolution of I.

The objective of this study was to examine the solubilization and dissolution of I in the presence of surfactants above and below their critical micelle concentrations (cmc). These data were then used to design a dissolution test for capsules of I.

MATERIALS AND METHODS

Materials - The following chemicals were used as received: sodium cholate (SC) (Eastman Kodak Co.); sodium dodecylsulphate (SDS) (Aldrich Chem. Co.); benzalkonium chloride (BAC) (Mason Chemicals); Polysorbate 80 (ICI Americas Inc.); polyoxyethylene (23) lauryl ether (POE lauryl ether) (Fisher Scientific Co.).

Solubility Determinations - The solubility of I at 26° and several surfactant concentrations was

determined by equilibrating excess solid I with solutions of the surfactants on a rotating device. It was observed that equilibration took a very long time - between 4 to 6 weeks - in water and at low surfactant concentrations. This points out the importance of confirming equilibration when carrying out solubility determinations on poorly soluble compounds. Equilibration was faster at high concentrations of surfactants where the solubility of I was increased. The solutions were then filtered through a 0.45μm filter, appropriately diluted, and assayed by either UV spectrophotometry or HPLC.

Intrinsic Dissolution Rate Determinations - The apparatus consisted of a covered water-jacketed beaker maintained at 37 ± 0.2° containing 800 ml of dissolution medium. Individual discs of about 300 mg of I were compressed at 5000 psi in a die using a hydraulic press[3]. The discs were 1.3 cm in diameter, and no capping or chipping was observed. The die containing the discs was mounted on a shaft that could be rotated by an overhead synchronous motor of variable speed[4]; the rotational speed was calibrated using a tachometer[5]. The die assembly was lowered into the dissolution medium to the same depth each time, and a timer started. Samples were withdrawn at various times, filtered, appropriately diluted, and assayed either by UV spectrophotometry or HPLC.

USP Dissolution Measurements - A USP six-spindle dissolution apparatus[6] was used with a paddle rotating at 50 rpm. The capsules were weighted down with copper wire and dropped into 900 ml of the dissolution medium. Samples were withdrawn, filtered

through a 2 μm filter, and assayed spectrophotometrically[7]. Temperature was maintained at 37°. The capsule shell and excipients did not interfere with the assay. All concentrations were corrected for volume changes occurring due to sampling.

Analysis of Samples -

Spectrophotometry: I has a UV spectrum with a maximum of 254 nm in water, where the molar absorptivity is 2.1×10^4 liter $mole^{-1}$ cm^{-1}. Thus, adequate sensitivity could be obtained for solubility and dissolution studies. However, P80 and BAC interfered with spectrophotometric detection, and an HPLC assay had to be developed for I in the presence of these surfactants.

HPLC: The method employed a chromatograph with a variable wavelength detector[8] and a 10μm C-18 column. The mobile phase was 80:20 methanol:water and gave a retention time of 5.6 minutes for I. Quantitation was by the use of external standards. Both BAC and P80 came out in the unretained peak.

Filter Adsorption: Since I is hydrophobic, it adsorbs onto filters used for solubility and dissolution samples. As much as 20% of the drug could be lost from aqueous solution on filtration; the actual amount lost depended on the concentration of I and the nature and surface area of filter. The presence of surfactants in solution reduced the amount of I lost on filtration. Presaturation of the filter with about 10 ml of the solution being filtered, or a solution of similar concentration, was necessary. A highly concentrated solution of I could not be used to presaturate filters because this caused solutions to increase in concentration on filtration.

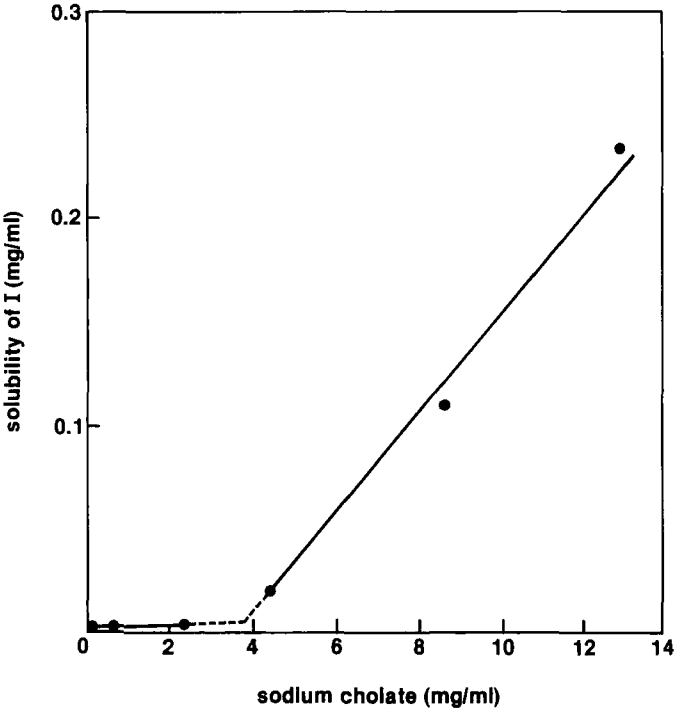


FIGURE 1

Solubility of I as a function of sodium cholate concentration at 26°.

Disintegration Testing: Some capsules and capsule cores were tested for disintegration in water and surfactant solutions in a USP disintegration apparatus[9].

RESULTS AND DISCUSSION

Solubility in Surfactant Solutions - The solubility of I at 26° was determined in solutions of five surfactants. The objective of examining these surfactants was to i) determine what effect the structure and charge type had on solubilization and,

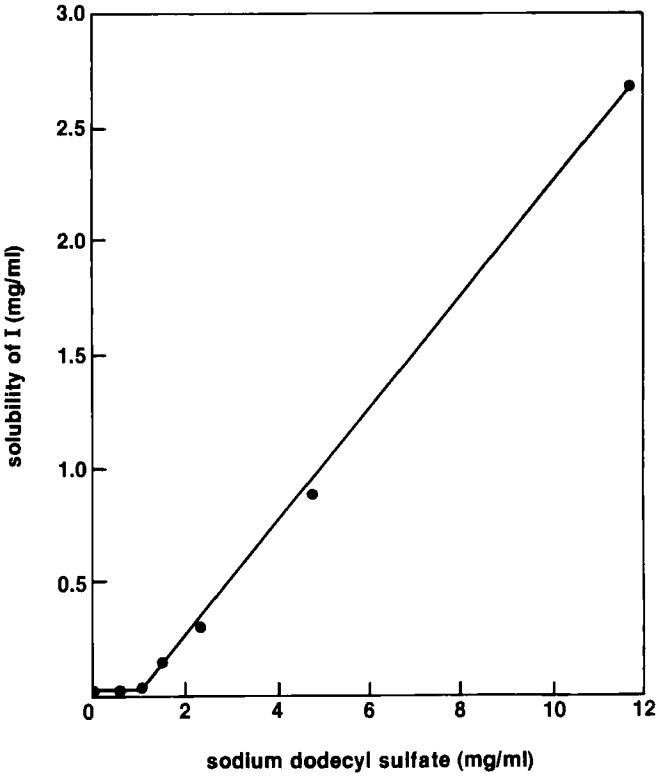


FIGURE 2

Solubility of I as a function of sodium dodecyl sulfate concentration at 26°.

ii) to select a suitable surfactant for use in USP dissolution test. Figs. 1-5 show the solubilities of I in the various surfactant solutions. The equilibrium solubility in water at 26° is 0.006 mg/ml (2.65×10^{-5}M). Very small or no increases in solubility are seen below the cmc's of the surfactants; solubilization, therefore, occurs in the micelles. The solubilization efficiency of each surfactant (moles I/mole surfactant) can be

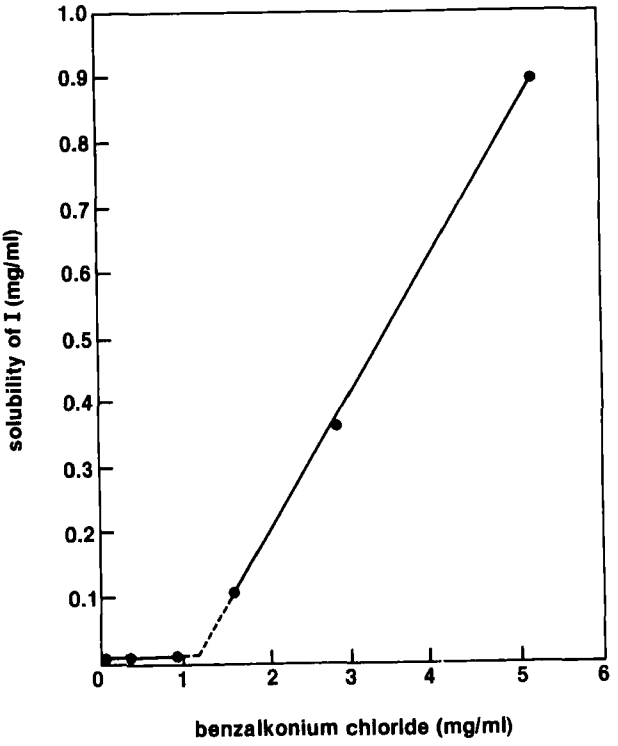


FIGURE 3

Solubility of I as a function of benzalkonium chloride concentration at 26°.

calculated from the slopes of the above figures. These values are shown in Table 1.

The solubilizing efficiency of these surfactants varies considerably, with the non-ionic surfactants being more effective.

Sodium cholate would have been the most physiologically relevant surfactant for dissolution studies; however, the solubility enhancement in sodium cholate was not large enough for the purposes of an in vitro dissolution test. Sodium dodecyl sulfate was the next choice since it did

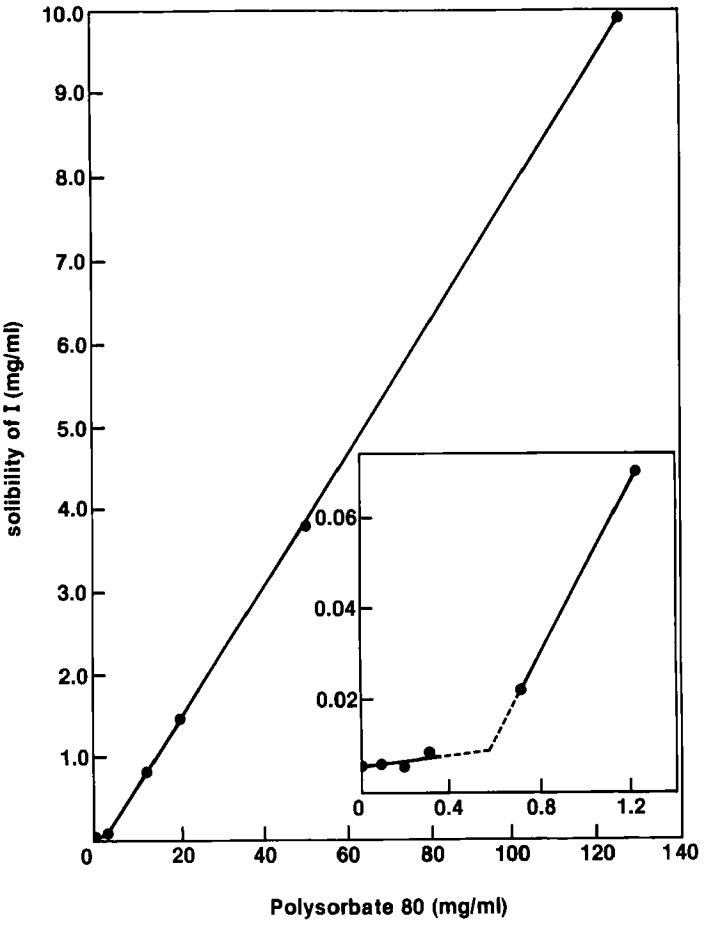


FIGURE 4

Solubility of I as a function of Polysorbate 80 concentration at 26°.

not interfere with the UV spectrum of I at the concentrations studied and gave good solubility enhancements of I.

Intrinsic Dissolution in Water - The intrinsic dissolution of I in water at 37° was studied by the rotating disc method. Sink conditions were maintained and the dissolution rates examined at various rotational speeds.

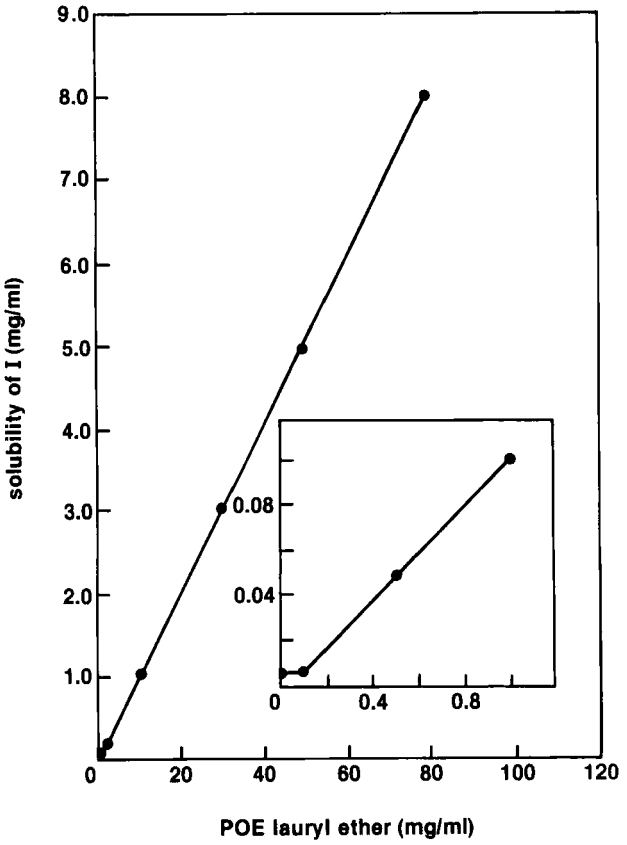


FIGURE 5

Solubility of I as a function of POE lauryl ether concentration at 26°.

TABLE 1

Solubilization Efficiency of Surfactants for I

Surfactant	[I]/[surfactant] (w/w)	moles I/ mole surfactant
Sodium cholate	0.0252	0.0479
SDS	0.257	0.328
BAC	0.0202	0.0322
Polysorbate 80	0.0794	0.460
POE lauryl ether	0.100	0.686

Under these conditions, the dissolution rate is given by Eq. 1 if the dissolution process is diffusion controlled(9).

$$J = \frac{A\ C_s}{1.612\ D^{-2/3}\ \nu^{1/6}\ \omega^{-1/2}\ V} \qquad \text{(Eq. 1)}$$

where: J = dissolution rate (moles/sec)
A = surface area of disc (cm^2)
D = diffusion coefficient (cm^2/sec)
ν = kinematic viscosity (cm^2/sec)
ω = angular velocity (radians/sec)
C_s = saturation solubility (moles/liter)
V = volume of dissolution medium (liters)

The value of D was estimated to be 5.4×10^{-6} cm^2/sec based on the Stokes-Einstein equation. The value of 9.77×10^{-3} stokes was used for ν(10), and the solubility of I at 37° was measured to be 4.42×10^{-5}M. These numbers were used to obtain an estimate of the expected dissolution rate as a function of rotation speed when plotted according to Eq. 2.

$$J/A = 0.62\ D^{2/3}\ \nu^{-1/6}\ {}_sC \cdot \omega^{1/2}\ V^{-1} \qquad \text{(Eq. 2)}$$

Fig. 6 shows a plot of the estimated line and the actual data. The data appears to fit the Levich diffusion model and the estimates used above seem to be reasonably valid. The scatter in the data is due to the very low concentrations of I present in solution under sink dissolution in water, resulting in a lower than desirable analytical precision.

Intrinsic Dissolution in Aqueous SDS Solutions - Fig. 7 shows the intrinsic dissolution rate of I at 37° and 100 rpm as a function of SDS concentration in

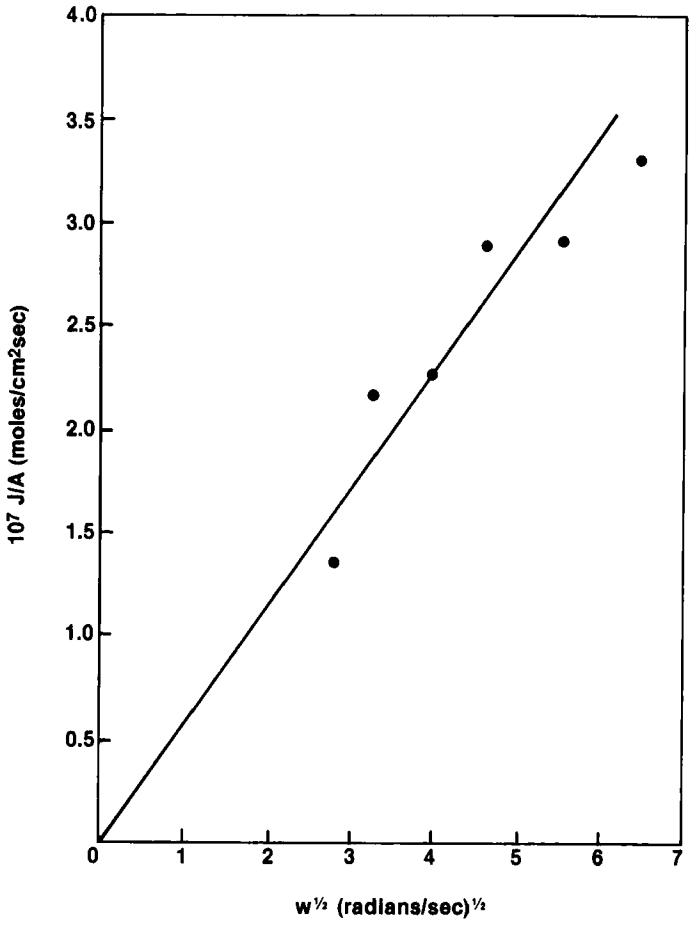


FIGURE 6

Levich plot for the dissolution of I in water at 37°. Data plotted according to Eq. 2. The line is the theoretical profile and the points are experimental values.

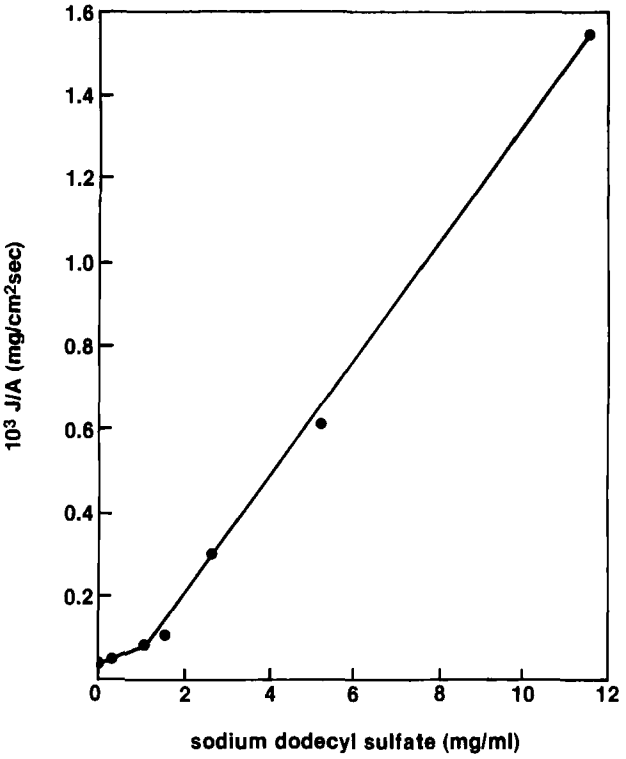


FIGURE 7

Intrinsic dissolution rate as a function of sodium dodecyl sulfate concentration at 37° and 100 rpm.

the dissolution medium. The plot shows a small increase in dissolution rate below the cmc, which can be attributed to better wetting of the solid surface due to the presence of SDS. Above the cmc, the major factor in the large increase of dissolution rate is the solubilization of I by SDS. As has been observed by several other workers, the increase in intrinsic dissolution rate is smaller than that expected based on the increase in solubility observed. This has been attributed(11,12) to the smaller diffusion

coefficient of the micelle-solubilized solute as compared to free solute.

Dissolution of Capsules in SDS Solutions - A dissolution test was to be designed for 300 mg capsules of I. The solubility of I at 37° in water (0.0096 mg/ml) corresponds to about 3% of the capsule contents dissolved in 900 mls. However, since these capsules are almost completely bioavailable, there is no dissolution problem in vivo. Thus an appropriate dissolution test had to be designed that gave complete, reproducible dissolution in a reasonable length of time. A 2.5% solution of SDS was first investigated as a dissolution medium for capsules of I. Results were disappointing; dissolution rates were increased but not substantially. It was observed that the SDS appeared to inhibit the disintegration of the capsules, resulting in slow dissolution.

Disintegration of Capsules of I in SDS Solutions - Generally it is expected that disintegration times of hydrophobic substances in surfactant solutions will be smaller than in water due to lowering of surface tension and improved wetting(13). Increase in disintegration times in the presence of surfactants has been generally observed for hydrophilic substances(14,15) and is dependent on the surface charge of the solid and the ionic nature of the surfactant. SDS, when incorporated into tablets, is reported to have variable effects on tablet disintegration(16). Polysorbate 80 has been shown to enhance the dissolution of one formulation of prednisolone tablets but retard the dissolution of another formulation(8). A possible interaction between the surfactant and some tablet excipient was advocated. The incorporation of Polysorbate 80 in

TABLE 2

Disintegration Times for Capsules of I

Disintegration Medium	Disintegration Time/min.
Water	4.0
2.5% SDS*	> 40
0.15% POE lauryl ether	2.0
1.5% POE lauryl ether	2.0

* with and without capsule shell

sulphanilamide tablets was found to repress swelling of starch grains and thus retard disintegration(17).

This suggested that in the system being examined, SDS may be interacting with a component of the capsule formulation to retard disintegration. Since the formulation had been compressed into a plug before filing into the capsule, disintegration with and without the capsule shell could be studied. As a comparison, disintegration in water and in POE lauryl ether was also examined. The data are shown in Table 2.

Disintegration was enhanced in POE lauryl ether solutions, at concentrations 10-fold and 100-fold greater than the cmc. In SDS solutions at a concentration 10-fold the cmc, disintegration times were considerably longer for the plug (with and without the capsule shell) than in water. When the plugs were gently ground up to simulate disintegration and then placed in the dissolution bath containing SDS solutions, the dissolution rate was enhanced.

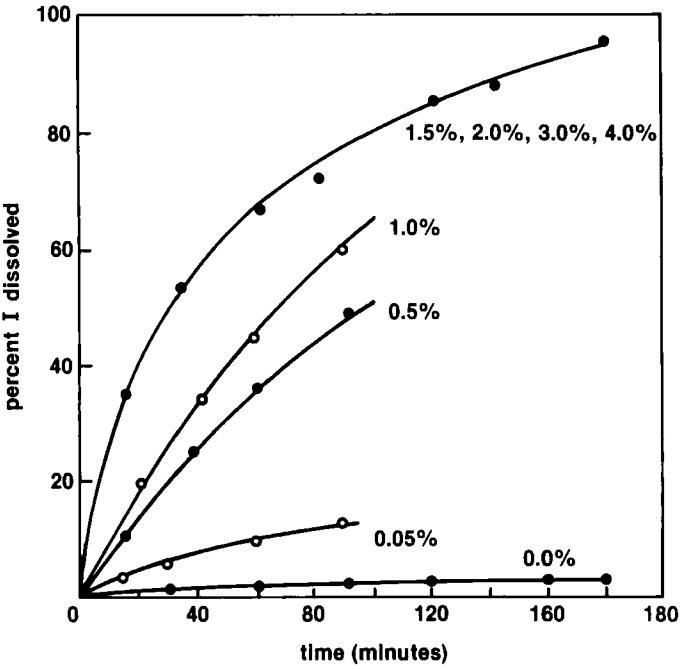


FIGURE 8

Dissolution profiles of 300mg capsules of I with various concentrations of POE lauryl ether in the medium.

It is possible that the SDS interacts with the magnesium stearate used as a lubricant in the formulation to form magnesium lauryl sulfate. It has been reported(18) that magnesium lauryl sulfate, when used as a lubricant, inhibits disintegration to a lesser degree than does magnesium stearate. However, if the magnesium lauryl sulfate is formed on the surface of the plug and coats it, disintegration could be inhibited. In addition, sodium sulfate has been reported to inhibit the gelatinzation of starch by competing for available water(19). Since starch is the disintegrant present in the capsule formula-

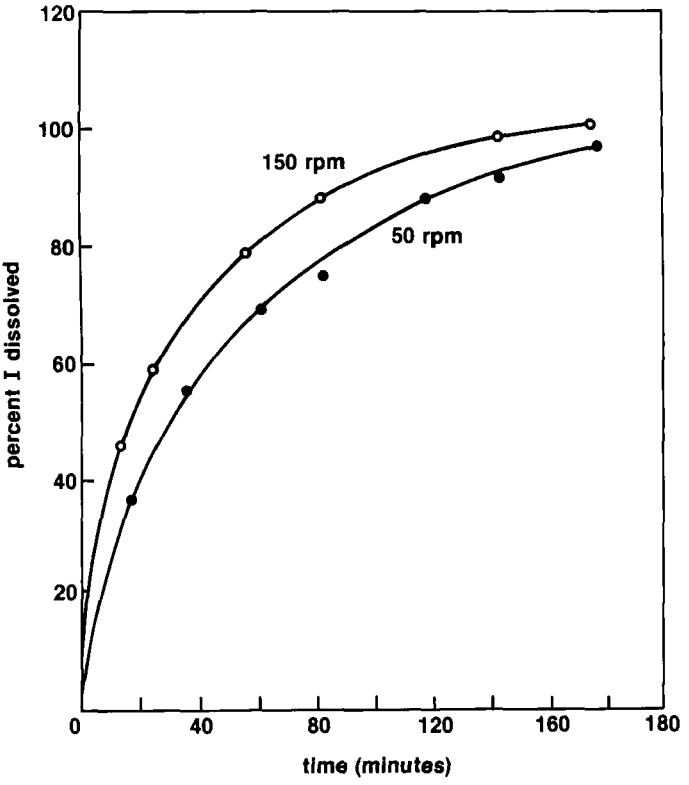


FIGURE 9

Effect of paddle rotation speed on dissolution of 300mg capsules of I in 1.5% POE lauryl ether.

tion, it is conceivable that SDS, which is also a sulfate salt, may behave in a similar manner. However, SDS when included in tablets as a lubricant has been reported to enhance dissolution rates in formulations containing starch(20). The disintegration problem in SDS solutions was not pursued further, and this surfactant was abandoned as a possible dissolution medium.

Dissolution of Capsules in POE Lauryl Ether Solutions - POE lauryl ether was examined as a dissolution medium for capsules. Fig. 8 shows the dissolution profiles at 50 rpm as a function of surfactant concentration. At concentrations above 1.5% POE lauryl ether, no further

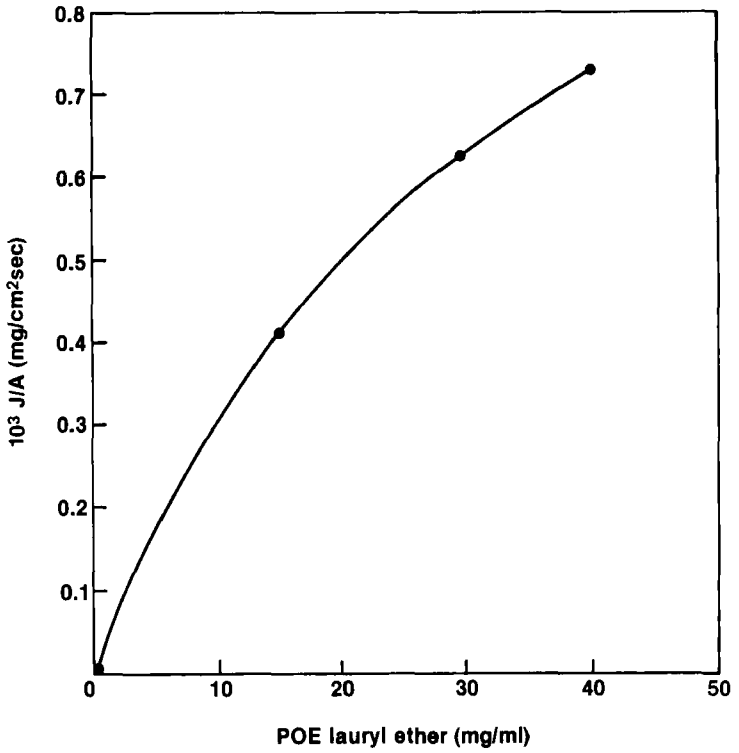


FIGURE 10

Intrinsic dissolution rates of I as a function of POE lauryl ether concentration at 37° and 50 rpm.

increase in capsule dissolution rate is observed. The reduced diffusion coefficient of the micelle-solubilized species has already been suggested. In addition, the viscosity increase, altered hydrodynamics, and the possible structuring of the solution at high surfactant concentrations may be responsible for the observations. A concentration of 1.5% POE lauryl ether was chosen as optimum for the dissolution of capsules. A small but significant increase in dissolution rate was observed with an increase in

paddle speed to 150 rpm, as seen in Fig. 9.

Intrinsic Dissolution in POE Lauryl Ether Solutions - The intrinsic dissolution of I was examined in POE lauryl ether solutions at these concentrations to see whether the same trend could be observed. The data are shown in Fig. 10 for the dissolution at 50 rpm and 37°. The dissolution rate is not a linear function of surfactant concentration and indicates a levelling off of the dissolution rate. Such levelling off of dissolution rates at high surfactant concentration has been observed for benzoic acid(21), and was attributed to the lower diffusion coefficient of the micelle solubilized solute. Again, viscosity, altered hydrodynamics and medium effects may also be operating at these large surfactant concentrations.

CONCLUSIONS

Compounds like I, on the basis of solubility studies, may indicate potential bioavailability problems and a formulator might consider altering the formulation to improve dissolution and therefore bioavailability. The presence of physiological surfactants in the gastrointestinal tract can have a dramatic effect on the dissolution and absorption of poorly water-soluble compounds. The inclusion of surfactants in the dissolution medium is a rational approach to designing a dissolution test for such compounds. However, it is impossible to reproduce the exact conditions of the gastrointestinal tract in an *in vitro* dissolution system. Non-physiological surfactants at suitable concentrations may have to be selected in order to give a dissolution test that is practical to use on a routine basis as a quality

control tool. Thus, physiological realities have to be balanced with practical considerations in order to develop a suitable dissolution test.

The authors do not intend to propose that all dissolution tests include a surfactant in the medium. However, for poorly water soluble drugs like I, where a simple dissolution test in water is useless and is not indicative of *in vivo* behavior, the inclusion of surfactants in the dissolution medium deserves serious consideration.

ACKNOWLEDGMENTS

The authors thank Ms. Susan Lawrence for her patience in typing this manuscript.

FOOTNOTES

[1] United States Patent 3,801,654; Boehringer Ingelheim GmbH
[2] unpublished results
[3] Fred S. Carver, Inc.
[4] G. K. Heller Corp.
[5] Power Instruments, Inc.
[6] Distek Inc. Model 2000
[7] Hewlett Packard 9845 Diode Array Spectrophotometer
[8] Waters, Inc.
[9] Erweka Apparatebau

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