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# Effects of solubilization on drug diffusion

J. R. BLOOR AND J. C. MORRISON

*School of Pharmacy, Portsmouth Polytechnic, Park Road, Portsmouth, Hants, PO1 2DZ, U.K.*

The diffusion of ephedrine, sulphathiazole, chloramphenicol, paracetamol, isoniazid and amphetamine in solutions of Tween 40, Tween 80 and cetomacrogol 1000 have been studied. With the exception of isoniazid, the observed diffusion coefficients, corrected for resistance to flow, depend upon the surfactant used and both the drug and surfactant concentration. The effect of drug solubilization upon the diffusion coefficient is also discussed.

The absorption of many drugs across biological membranes occurs by passive diffusion from a region of high to one of low concentration. Riegelman & Crowell's (1958) results suggested that the diffusion of drugs to the absorption site is the limiting factor in rectal absorption. Similarly, Gemmel & Morrison (1957) suggested that a knowledge of the steps limiting the rate of drug transfer through topical applications is valuable in assisting the formulation of such applications. Although it has been shown by Nordqvist (1953) using nerve block anaesthesia, Tanz (1951) by induction block of frog nerve fibres and Sobel (1948) by absorption of solubilized vitamins that the presence of surfactants enhanced pharmacological activity; Kakemi, Arita & others (1965) claimed a reduction in such activity. We have therefore examined the effects of three non-ionic surfactants on drug diffusion with the aim of clarifying the mechanisms by which the surfactants influence drug transport and absorption processes.

## MATERIALS AND METHODS

*Materials.* Tween 40, a polyoxyethylene sorbitan monopalminate, Tween 80, the corresponding mono-oleate and cetomacrogol 1000 were characterized by nuclear magnetic resonance spectroscopy according to Rhodes (1967).

Ephedrine, sulphathiazole, chloramphenicol, paracetamol and isoniazid were characterized by melting point (B.P. 1968). The purity of amphetamine was assessed by measuring its refractive index at 25°. The surfactants and drugs complied with the relevant official or manufacturer's specifications.

Spectrophotometrically pure cyclohexane was used as received.

### *Assay of drugs in the presence of non-ionic surfactants*

A scan of absorption against wavelength using a Unicam SP800 recording spectrophotometer showed essentially constant absorption over the region 240 to 350 nm for the surfactants. The absorption of the surfactant in the presence of a drug was effectively eliminated by subtracting the absorption at a spectral shoulder of the drug from that at the spectral peak (Table 1). The solutions contained either hydrochloric acid or sodium hydroxide (0·005N) to suppress ionization of the respective drugs.

### *Measurement of diffusion coefficient*

The diffusion cell used was based on the open ended capillary technique (Castleden & Fleming, 1966) with capillaries 2–2·5 cm long and 0·2 cm in diameter sealed at

Table 1. *Ultraviolet spectrophotometric assay of drugs.*

| Drug | Cell length (mm) | Diluent (0·005N) | Wavelengths (nm) | | Concn range (mg/litre) | Correlation coefficient |
|---|---|---|---|---|---|---|
| | | | Maximum | Shoulder | | |
| Ephedrine .. | 40 | NaOH | 257·0 | 266·0 | 0–200 | 0·99 |
| Sulphathiazole .. | 40 | HCl | 283·5 | 305·0 | 0–5 | 0·99 |
| Chloramphenicol | 10 | HCl | 277·5 | 310·0 | 0–32 | 0·99 |
| Paracetamol .. | 10 | HCl | 243·0 | 270·0 | 0–20 | 0·99 |
| Isoniazid .. .. | 10 | HCl | 265·0 | 285·0 | 0–32 | 0·99 |
| Amphetamine .. | 40 | NaOH | 257·5 | 266·0 | 0–225 | 0·99 |

one end with a globule of glass, care being taken to avoid distortion of the bore. The lengths were measured using a travelling microscope. The concentration of drug initially in each capillary was found by filling and centrifuging out the contents after attaining thermal equilibrium and making up to a fixed volume. The capillaries were then refilled and completely immersed to a depth of a few mm in a securely clamped three-necked flask containing 1 litre of degassed bulk solution at constant temperature ($25 \pm 0{\cdot}1°$) and that temperature was used for all subsequent work. At the end of the recorded diffusion period the capillaries were carefully withdrawn from the bulk solution, wiped free of surplus liquid and their contents plus washings determined as before. The bulk solutions were not stirred.

*Determination of the viscosity of the diffusion systems*

The viscosity of the most concentrated surfactant solutions with and without each drug were determined in both British Standard types A and B glass capillary viscometers using the procedure of British Standards Specification 188, 1957. The viscosities recorded were independent of the viscometer used which indicated that the viscosities were not related to the rates of shear of the two viscometers. Within these limits all the surfactant solutions may be assumed Newtonian. A type-A viscometer was then used for all subsequent measurements. The weight per ml of each solution was determined with a density bottle.

*Determination of solubilization*

*Partition analysis.* Ephedrine was partitioned between cyclohexane and the surfactant solutions according to the technique of Karush (1951). The two phases were gently agitated at a frequency of 12 cycles/min and under these conditions equilibration was achieved in 8 h. At equilibrium the organic phase was discarded and the aqueous phase assayed spectrophotometrically after suitable dilution.

*Equilibrium dialysis and solubility experiments.* Dialysis was examined using a cell as described by Patel & Foss (1964) and Humphreys & Rhodes (1968). The membrane used was Portex C nylon film (Portland Plastic Ltd., Hythe, Kent) of thickness 0·002 inch and width 5 inch. The cells were agitated laterally and one-ml samples were removed at intervals and assayed spectrophotometrically after suitable dilution. Equilibration time varied greatly according to the drug, being a maximum of 500 h for ephedrine and a minimum of 100 h for sulphathiazole.

## RESULTS AND DISCUSSION

The diffusion coefficient, D, can be calculated from the following equation (Tuwiner, 1962).

$$C_T = 8\frac{Co}{\pi^2}\frac{l}{(2n+l)^2}\exp\frac{-D(2n+l)^2}{4l^2}\pi^2 t \quad .. \quad .. \quad .. \quad (1)$$

where $C_T$ is the average concentration assay of the solution at the end of the experiment, Co is the initial concentration, $l$ is the capillary length (cm) and t is the time of diffusion (s).

The series converges satisfactorily and only the first term need be considered (Wang, 1952) when

$$\frac{Dt}{l^2} > 0{\cdot}2 \quad .. \quad .. \quad .. \quad .. \quad .. \quad (2)$$

The open ended capillary method and experimental technique were checked by measuring the differential diffusion coefficient of 3·5M sodium chloride in a 1 litre bulk of 2·5M sodium chloride using an Interference Refractometer (Hilger and Watts) for the quantitative sodium chloride assays. The diffusion coefficient we found ($1{\cdot}58 \pm 0{\cdot}04 \times 10^{-5}$ cm$^2$ s$^{-1}$) is slightly lower than that of Mills & Adamson (1955) ($1{\cdot}63 \pm 0{\cdot}06 \times 10^{-5}$ cm$^2$ s$^{-1}$). These authors conceded that their results were high compared with the value given by Stokes (1950) ($1{\cdot}54 \times 10^{-5}$ cm$^2$ s$^{-1}$) using the diaphragm method, therefore the sodium chloride diffusion coefficient reported here is evidence that the apparatus is capable of providing data consistent with other workers and methods. In this work a stirring rate of 100 rev/min gave a differential diffusion coefficient of sodium chloride of $1{\cdot}84 \times 10^{-5}$ cm$^2$ s$^{-1}$ and reducing the speed to 50 rev/min gave $1{\cdot}58 \times 10^{-5}$ cm$^2$ s$^{-1}$. Further reduction of the stirring speed had no significant effect on the results. This finding was verified in both aqueous and surfactant systems and led to the abandonment of the stirrer for the bulk solution.

$$D_V = \frac{D}{(1-\phi)} \quad .. \quad .. \quad .. \quad .. \quad (4)$$

where $D_V$ is the corrected diffusion coefficient and $\phi$ is a constant having a theoretical value of 1·5 for spheres.

The drugs selected had a wide range of aqueous solubilities and showed an equally wide response to the presence of surfactant. With the exception of the isoniazid system the corrected diffusion coefficients depend upon the surfactant and both drug and surfactant concentration. In the systems demonstrating accelerated diffusion (Fig. 1) the corrected diffusion coefficient rises both as the drug concentration and surfactant concentration rise. The peak in the uncorrected diffusion coefficient in the region of 2 to 3% surfactant is in agreement with the findings of Barker, Dekay & others (1956) who studied the release of iodine from creams stabilized with Tween 40. The graph of the diffusion coefficient corrected for the resistance to flow does not show this peak suggesting that there is a factor facilitating diffusion in these systems masked to a degree by relatively high viscosity of the surfactant solutions.

The results presented in Fig. 2 at a surfactant concentration of 5% illustrate that the dialysis and partition analysis techniques are complimentary. The results from the dialysis studies also show that the solubilization of sulphathiazole, chloramphenicol and paracetamol in the non-ionic surfactants used are governed by a form of the distribution law (Humphreys & Rhodes, 1968). It can be seen from Figs 2 and 3 that as the concentration of ephedrine and amphetamine increases in the surfactant systems the relative quantity of solubilized drug decreases. This type of relation is indicative of an adsorption phenomenon (Tanford, 1961).

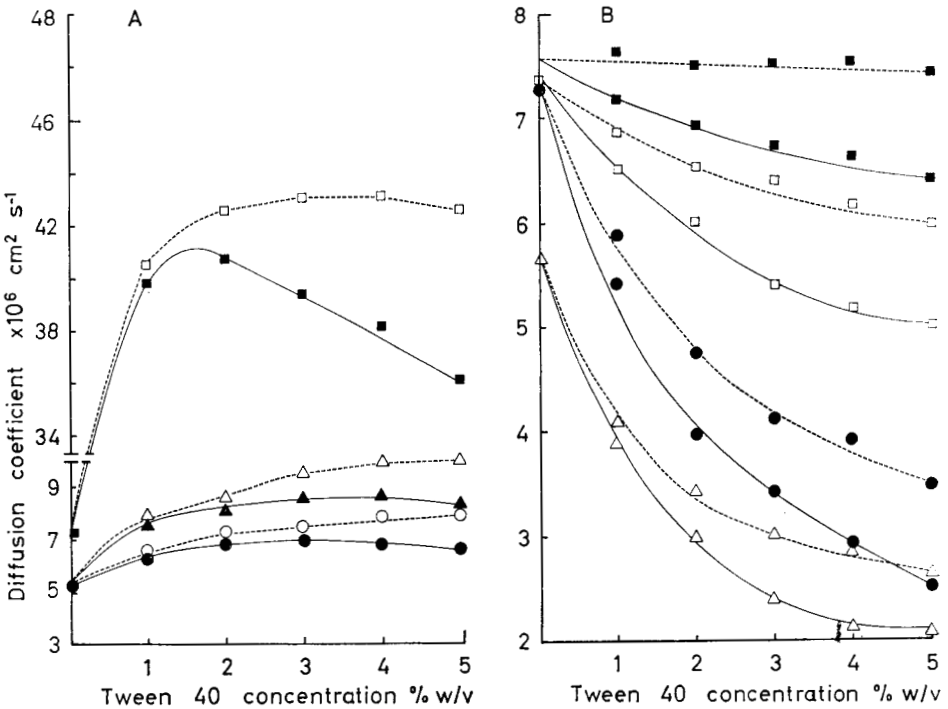


FIG. 1. Diffusion coefficients of selected drugs in Tween 40 solutions at 25°.
—— Observed diffusion coefficient. – – – Diffusion coefficient corrected for micellar volume fraction effects.
A: ■, Amphetamine 10 mg/ml; ▲, ephedrine 10 mg/ml; ●, 2·2 mg/ml.
B: ■, Isoniazid 40 mg/ml; □, paracetamol 14 mg/ml; ●, sulphathiazole 0·3 mg/ml; △, chloramphenicol 2·5 mg/ml.

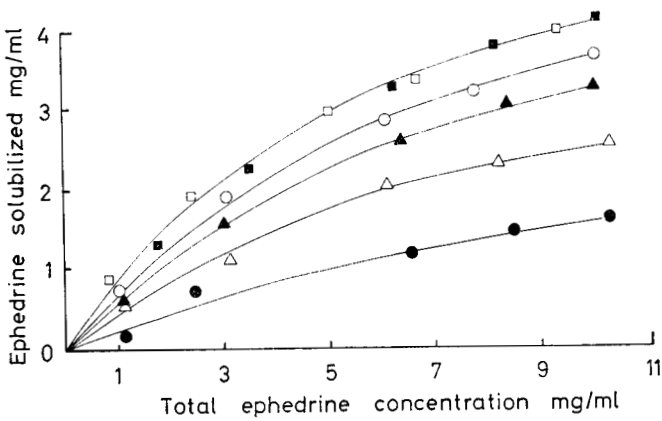


FIG. 2. Solubilization isotherms of ephedrine in Tween 40 by partition analysis at 25°. [Tween 40: ●, 1%; △, 2%; ▲, 3%; ○, 4%; □, partition analysis, 5% Tween 40; ■, equilibrium dialysis 5% Tween 40.
Solubility of ephedrine in water at 25° is 31·3 mg/ml.

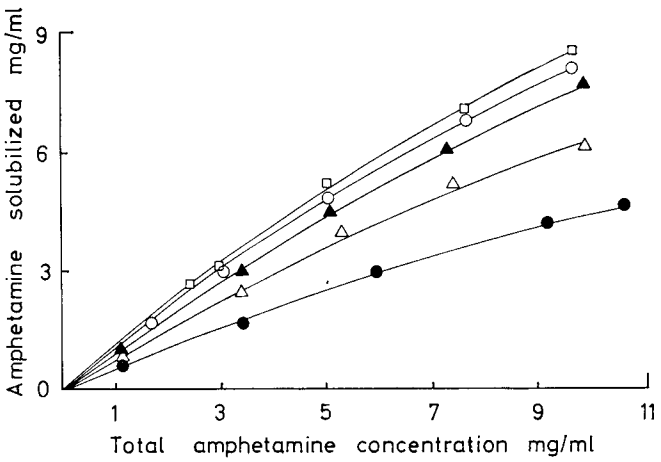


FIG. 3. Solubilization isotherms of amphetamine in Tween 40 solutions by equilibrium dialysis at 25°. Tween 40: ●, 1%; △, 2%; ▲, 3%; ○, 4%; □, 5%.
Solubility of amphetamine in water at 25° is 21·7 mg/ml.

Table 2. *Summary of viscosity data.*

| System | Surfactant concentration (%) | Relative viscosity | Micellar volume fraction |
|---|---|---|---|
| Ephedrine 10 mg/ml Tween 40 .. .. | 1 | 1·063 | 0·0225 |
| | 3 | 1·214 | 0·0632 |
| | 5 | 1·381 | 0·0980 |
| Ephedrine 2·2 mg/ml Tween 40 .. .. | 1 | 1·055 | 0·0190 |
| | 3 | 1·179 | 0·0545 |
| | 5 | 1·324 | 0·0895 |
| Sulphathiazole 0·3 mg/ml Tween 40 .. | 1 | 1·074 | 0·0265 |
| | 3 | 1·215 | 0·0677 |
| | 5 | 1·372 | 0·0963 |
| Chloramphenicol 2·5 mg/ml Tween 40 .. | 1 | 1·073 | 0·0255 |
| | 3 | 1·222 | 0·0649 |
| | 5 | 1·370 | 0·0960 |
| Paracetamol 14 mg/ml Tween 40.. .. | 1 | 1·059 | 0·0233 |
| | 3 | 1·193 | 0·0599 |
| | 5 | 1·327 | 0·0885 |
| Amphetamine 10 mg/ml Tween 40 .. | 1 | 1·072 | 0·0252 |
| | 3 | 1·226 | 0·0660 |
| | 5 | 1·416 | 0·1046 |
| Isoniazid 40 mg/ml Tween 40 .. .. | 1 | 1·054 | 0·0194 |
| | 3 | 1·192 | 0·0579 |
| | 5 | 1·367 | 0·0958 |

The constant average diffusion velocity observed in any system is a function of the viscosity of that system and a correction for the viscosity must be made to allow comparison between systems under investigation. In the systems examined the resistance to flow originates primarily from the flow lines produced by the Brownian motion of neighbouring micelles and the accompanying movement of the hydrated

Table 3. *Summary of solubilization data.*

| Drug | Surfactant | Distribution coefficient | Drug solubilization in 1% surfactant (mg/ml) |
|---|---|---|---|
| Sulphathiazole 0·3 mg/ml .. .. | Tween 40 | 39·95 | 0·086 |
| Chloramphenicol 2·5 mg/ml .. | Tween 40 | 21·33 | 0·44 |
| Paracetamol 14 mg/ml .. .. | Tween 40 | 8·64 | 1·11 |
| Ephedrine 10 mg/ml .. .. | Tween 40 | — | 1·24 |
| Ephedrine 2·2 mg/ml .. .. | Tween 40 | — | 0·41 |
| Amphetamine 10 mg/ml .. .. | Tween 40 | — | 4·22 |
| Sulphathiazole 0·3 mg/ml .. .. | Cetomacrogol 1000 | 21·50 | 0·053 |
| Sulphathiazole 0·3 mg/ml .. .. | Tween 80 | 41·35 | 0·088 |
| Isoniazid 40 mg/ml .. .. | Tween 40 | — | 0 |

polyoxyethylene chains. The extent of this resistance is related to the volume fraction of the micelles which can be calculated from the Guth & Simha (1936) equation

$$r = 1 + 2{\cdot}5\phi + 14{\cdot}1\phi^2 \qquad (3)$$

where r is the relative viscosity and $\phi$ is the micellar volume fraction. Using equation (3) for a multicomponent system the relative viscosity is the bulk viscosity divided by the viscosity of the solvent, which will contain some unsolubilized drug.

Relative viscosity and micellar volume fraction for the drugs in Tween 40 are given in Table 2.

In accordance with the theory of Wang (1954) the increase in diffusion coefficient, to make allowance for the mechanical obstruction of the micelles, is given by equation (4).

In a surfactant system the diffusion of a partially solubilized drug can be accomplished by two processes—one the result of random molecular motion following applications of Fick's law and the other by incorporation into the micelle which then diffuses subject to the physical parameters of the micellar structure and which may not be governed by the conventional laws of diffusion. A comparison of diffusion and solubilization data suggests that the diffusion coefficient of a drug in a solubilized system increases in comparison with the corresponding aqueous system when the total quantity of drug solubilized is great. Retarded diffusion is, in general, indicative of a poorly solubilized system. For example, sulphathiazole, a poorly solubilized drug (Table 3) showed a reduction in diffusion coefficient of 21, 28 and 30%, in relation to a pure water value of 7·55 $cm^2\ s^{-1}$, when dissolved in cetamacrogol, Tween 40 and 50 respectively. The diffusion coefficient of isoniazid, which from dialysis techniques was found not to be solubilized in Tween 40, was shown to be essentially constant after consideration of the effects of mechanical micellar obstruction.

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