

Adsorption of non-ionic surfactants at the griseofulvin–solution interface

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The adsorption from solution onto griseofulvin powder of a series of non-ionic detergents of the polyoxyethylene glycol mono alkyl ether type is described. Results are also given for polyethylene glycol 400 and a new detergent, pentaerythritol mono-*n*-octyl ether, whose synthesis and purification is reported. The effect of temperature on the adsorption is studied and possible explanations of the variation of adsorption with temperature are based on the orientation of the molecules at the interface; this is deduced from measured molecular areas.

Surfactants are of use in controlling the properties of powders to be formulated as suspensions. As well as affecting wetting of the powder, the adsorbed film of surfactant can control the physical stability of the suspension. Ionized surfactants can affect control by charge effects while non-ionic surfactants act through electrostatic and entropic factors. The contribution of electrostatic and entropic factors to the stabilization of emulsions by non-ionic surfactants has been investigated (Elworthy & Florence, 1969), but little work has been done on the mechanism of stabilization of pharmaceutical suspensions by non-ionic surfactants.

Few studies of adsorption of non-ionic surfactants from solution have been made: Corkill, Goodman & Tate (1966) used graphitized carbon black as adsorbent and short chain polyoxyethylene glycol ethers as adsorbates whilst Abe & Kuno (1961, 1962) studied the adsorption of octyl phenol non-ionics on carbon and calcium carbonate. Other authors have examined the adsorption of polyoxyethylene ethers on paraffin wax (Lange, 1960) and silver iodide particles (Mathai & Ottewill, 1962, 1966). In their 1966 paper, Mathai & Ottewill related the stability of the dispersion to the adsorption results.

Griseofulvin is virtually insoluble in water, and can be formulated as a suspension. In this paper the adsorption of seven non-ionic surfactants and a polyoxyethylene glycol from aqueous solution onto griseofulvin is reported.

EXPERIMENTAL

Materials

Griseofulvin was recrystallized from absolute ethanol, dried, and ground in a glass mortar. Coarse particles were removed on a mesh 120 sieve, and the fraction retained by the 170 mesh sieve was used. M.p. 497° K (British Pharmacopoeia gives m.p. 491°–497° K). Two batches were prepared, the particle size distribution being determined with a Model A Coulter Counter using 0.9% sodium chloride solution

with the addition of 0.05% cetomacrogol 1000 as the suspension medium, the suspension being irradiated ultrasonically just before sizing. The mean particle diameters were 4.3 and 5.2 μm respectively from which the mean volume surface diameters were calculated from the Hatch-Choate relation. Values of 1550 and 1310 m^2/kg were found for the specific surface areas.

Six of the surfactants used were polyoxyethylene glycol monohexadecyl ethers, i.e. C_{16}E_x . Texofor A10, A45 and A60 (Glovers Chemicals Ltd.) were characterized with $x = 10, 47$ and 62 ethylene oxide units respectively. Cetomacrogol 1000 B.P.C. (Macarthys Ltd.) contained 23 units. The ethylene oxide content was determined by nmr spectroscopy, according to Humphreys (1968). The synthetic surfactants were prepared according to Elworthy & Macfarlane (1962). C_{16}E_7 had m.p. 311°K (311.5°K), ethylene oxide content, by the method of Siggia, Stark & others (1958) 55.6%; C_{16}E_9 had m.p. 317°K (318°K), ethylene oxide content 62.07% (62.05%). Literature, or "required" analytical figures are given in brackets.

The remaining surfactant pentaerythritol mono-n-octyl ether (C_8P) was synthesized as follows (Barth, 1953).

A solution of 1 mol of paraformaldehyde in 0.925 mol n-octyl alcohol (10% by volume) was added to a solution of sodium hydroxide (0.35 mol) of n-octyl alcohol (1.625 mol) at 296°K . The remainder of the paraformaldehyde solution plus acetaldehyde (0.2 mol) was mixed and added slowly to the caustic solution.

The mixture was allowed to stand for 24 h, heated to 328°K , and stirred for 12 h. It was then neutralized with dilute hydrochloric acid, filtered and the excess octyl alcohol removed by vacuum distillation (13.3 Nm^{-2}). Methanol ($5 \times 10^{-4}\text{ m}^3$; 500 ml) and concentrated hydrochloric acid ($2 \times 10^{-6}\text{ m}^3$; 2 ml) were added to the residue and the resulting solution distilled slowly at 323°K to remove any formaldehyde as methylal.

Acetylation was accomplished by refluxing for 3 h with a slight excess of acetic anhydride (0.5 mol). Excess acetic acid was removed by distillation and any precipitated pentaerythritol tetra acetate filtered off.

The crude esters were distilled (6.66 Nm^{-2}) to yield four fractions with boiling ranges $333\text{--}358^\circ\text{K}$; $393\text{--}403^\circ\text{K}$; $403\text{--}421^\circ\text{K}$; and $441\text{--}445^\circ\text{K}$ respectively. Infrared examination showed the second, third and fourth fractions to have ether linkages. Fraction four was assumed to be the di-ether due to the magnitude of the 11.20 m^{-1} adsorption peak (ether peak) and also its higher boiling point. The spectra of fractions two and three were almost identical and those two fractions were combined as the crude tri-acetyl mono-ether. Saponification of the ester was effected by refluxing with sodium ethoxide in absolute ethanol (Wawzonek & Issidorides, 1953). The reactants were neutralized, filtered and distilled leaving a viscous residue which solidified on standing.

The impure material (2.5 g) was chromatographed on a mixed silicic acid/Celite column (27 g + 7 g) using benzene-acetone as solvent. The pure compound eluted by 5% acetone in benzene was dried and recrystallized from anhydrous ether to give a white solid m.p. 311°K , mol. wt. 247.8 (theoretical 248.3). $\text{C}_{13}\text{H}_{28}\text{O}_4$ requires C, 62.9; H, 11.4%. Found, C, 62.7 (62.9); H, 12.4 (11.4). The C_8P compound has been described in detail as it has not been previously prepared pure enough for surface chemical work. No minimum was observed in a surface tension-log concentration curve.

Polyoxyethylene glycol 400 (B.D.H.) was used as supplied.

Adsorption measurements

Griseofulvin (0.5 g) and surfactant solution ($1 \times 10^{-5} \text{ m}^3$; 10 ml) of known concentration were placed in a screw-capped bottle, which was shaken until the powder was dispersed. The suspension was irradiated for 15 s using an M.S.E. Ultrasonic generator, and allowed to equilibrate in a thermostat ($\pm 0.01^\circ$) for 16 h. The supernatant liquid was decanted, centrifuged and analysed by one of the methods listed below. Neither degassing the suspension before placing in the thermostat, nor varying the irradiation time had any effect on the amount adsorbed. Measurements made over 3 days indicated that adsorption was complete at 16 h.

Analytical methods

The presence of dissolved griseofulvin interfered with concentration measurements by interference refractometry. For analysis of C_{16}E_x compounds the iodine method of Ross & Olivier (1959) was adapted. A sample ($2 \times 10^{-6} \text{ m}^3$; 2 ml) of the surfactant solution was mixed with an aqueous iodine solution containing 200 mg dm^{-3} ($1 \times 10^{-6} \text{ m}^3$; 1 ml), and the extinction measured in 10 mm cells at 390 nm. Calibration graphs using known surfactant concentrations were linear in the concentration region of interest. The method is very sensitive, and concentrations of the order of $4 \times 10^{-7} \text{ mol dm}^{-3}$ can be determined.

For polyoxyethylene glycol 400 Milwidsky's (1969) method was used, the blue water-insoluble complex formed between the glycol and ammonium cobaltothiocyanate being estimated in 20 mm cells at 628 nm.

C_8P was estimated by Reid & Salmon's (1955) method.

RESULTS AND DISCUSSION

Representative isotherms for the C_{16}E_x series of surfactants (Figs 1 and 2) are of the Langmuirian type over the concentration range studied. The maximum amount of surfactant adsorbed was obtained from the plateau region of the isotherms. The region of maximum adsorption occurs in most cases at or close to the critical micelle concentration (shown by arrows on the Figures).

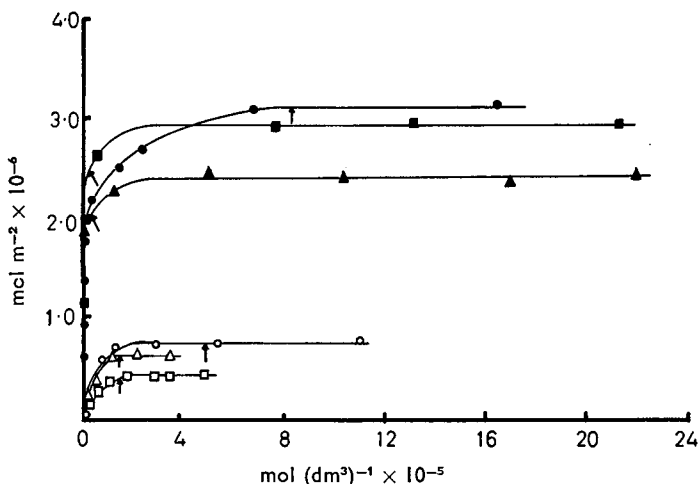


FIG. 1. Isotherms for the non-ionic surfactants adsorbed on griseofulvin at 298°K : ●, A10; ■, C_{16}E_7 ; ▲, C_{16}E_9 ; ○, Cetomacrogol; △, A45; □, A60. Arrows mark CMC.

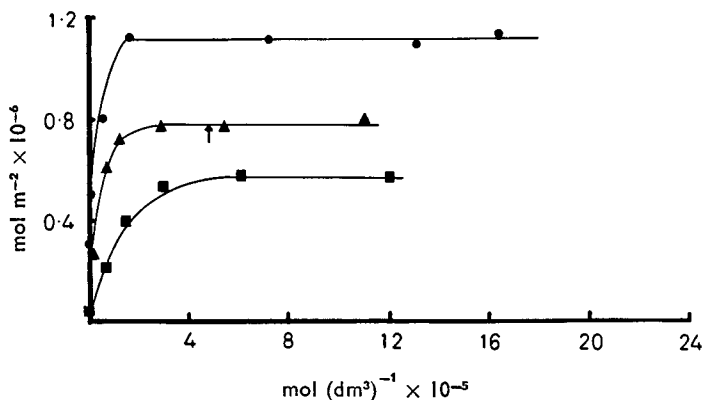


FIG. 2. Effect of temperature on the adsorption of cetomacrogol on griseofulvin: ●, 288° K; ▲, 298° K; ■, 308° K.

The isotherms for C₈P (Fig. 3) show a small and roughly constant adsorption at low concentrations, followed by a greatly increased adsorption, which is possibly due to multilayer formation. PEG 400 (Fig. 4) shows a similar behaviour, but with no secondary increase in adsorption over the concentration range used.

Temperature has a considerable effect on adsorption. For cetomacrogol (Fig. 2) an increase in temperature decreases adsorption and causes monolayer coverage to occur at higher equilibrium concentrations. This decrease in adsorption with rise of temperature is also shown by C₈P, C₁₆E₄₅, and C₁₆E₇. PEG 400 behaves differently—adsorption increasing with a rise in temperature (Fig. 4), and monolayer coverage shifting to lower equilibrium concentrations.

The PEG 400 results indicate that this head group (of the surfactants) has a tendency to adsorb on the griseofulvin surface. The area occupied by a Catalin model corresponding to PEG 400 is 1.50 nm², while the observed area/molecule at monolayer coverage is 2.96 nm², indicating that the glycol is likely to be adsorbed flat on the

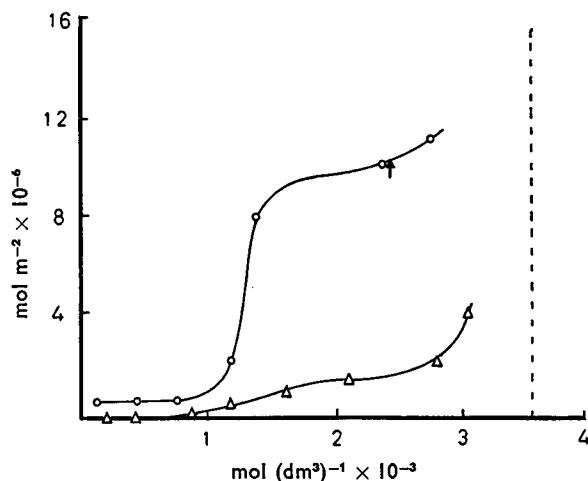


FIG. 3. Adsorption isotherms for C₈P at two temperatures: ○, 298° K; △, 308° K. The dotted line represents the phase boundary.

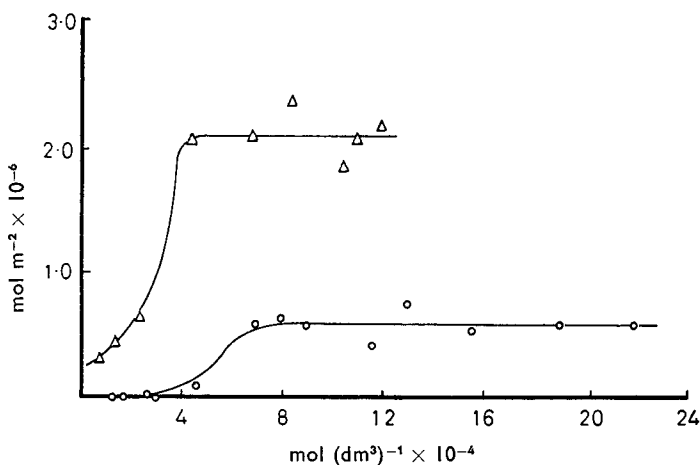


FIG. 4. Effect of temperature on the adsorption of polyethylene glycol 400: ○, 298° K; △, 308° K.

surface. When the hexadecyl chain is attached to one end of the PEG 400 chain (i.e. $C_{16}E_9$ or Texofor A10), the number of moles adsorbed at monolayer coverage increases, and the area/molecule decreases by factors of 4 to 5. This indicates that the hydrocarbon chain is adsorbed at the surface; if it were not, the area/molecule would not change significantly. Increasing the polyoxyethylene chain length of the surfactant has the effect of decreasing the maximum amount adsorbed and increasing the area/molecule (Table 1). It seems possible that the hydrocarbon chain is adsorbed end on to the surface, and that the polyoxyethylene chain bends towards the surface and is also attached to it.

The values calculated for the areas/molecule at the griseofulvin–solution interface are greater than those published for the closest packing at the air–water interface, e.g. cetomacrogol 2.13 nm^2 (1.20 nm^2), $C_{16}E_7$ 0.57 nm^2 (0.45 nm^2), and $C_{16}E_9$ 0.69 nm^2 (0.53 nm^2), the values in brackets being those for the air–water interface. This comparison indicates that the polyoxyethylene chain is contributing more to the area/molecule at the solution–solid than at the air–water interface, and also that the surfactants containing the shortest PEG chains are most closely packed; this is in accordance with the work of Corkill & others (1966). The increase of area/molecule

Table 1. Values of the maximum adsorbed and the areas/molecule for the compounds examined.

Compound	Maximum adsorbed ($\text{mol m}^{-2} \times 10^6$)			Area/molecule at the griseofulvin–solution interface nm^2		
	288° K	298° K	308° K	288° K	298° K	308° K
Texofor A10	—	3.12	—	—	0.52	—
Cetomacrogol 1000	1.12	0.78	0.57	1.48	2.13	3.43
Texofor A45	—	0.65	0.25	—	2.55	6.64
Texofor A60	—	0.44	—	—	3.77	—
$C_{16}E_7$	—	2.92	2.43	—	0.57	0.68
$C_{16}E_9$	—	2.39	—	—	0.69	—
PEG 400	—	0.56	2.11	—	2.96	1.27
C_8P	—	10.11	1.81	—	0.16	0.92

with polyoxyethylene chain length has also been shown by Abe & Kuno (1962) for nonyl phenols on carbon.

Fig. 5 shows the variation in maximum amount adsorbed with ethylene oxide chain length. Within experimental error, the synthetic surfactants $C_{16}E_7$ and $C_{16}E_9$ and the commercial surfactants $C_{16}E_{10}$, $C_{16}E_{45}$ and $C_{16}E_{60}$ fall on the same line which represents the change in adsorption with increasing length of ethylene oxide chain. This indicates that the width of the chain length distributions in the commercial surfactants does not have a marked effect on the adsorption. A similar conclusion has already been reached for adsorption of non-ionics on quartz (Dunning, 1957).

The shape of the isotherm for the pentaerythrityl ether C_8P (Fig. 3) differs considerably from those given by the other surfactants. The area/molecule at the griseofulvin-solution interface is 0.16 nm^2 compared with a value of 0.47 nm^2 at

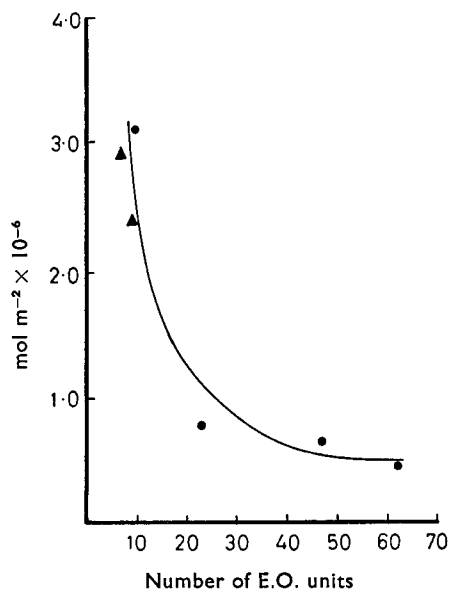


FIG. 5. Variation in maximum adsorbed with ethylene oxide chain length: ▲, Synthetic detergents; ●, Commercial detergents.

the air-water interface (Elworthy & Guthrie, unpublished), which suggests multilayer adsorption at the former interface. Sigmoid isotherms, similar to those given by C_8P have been found by Corkill & others (1966) and Kuno & Abe (1961) when adsorption was studied at concentrations close to a phase boundary. The phase boundary is shown in Fig. 3, and it is possible that surface nucleation leading to multilayer formation occurs. The decrease in adsorption with increased temperature may be due to thermal agitation opposing the tendency to multilayer formation.

Factors affecting the change of adsorption with temperature are likely to be complex, involving alterations of water structure around hydrocarbon chains, and the alteration of chain conformation. PEG 400 shows an increased adsorption as the temperature rises. This may be due to desolvation, or to increased thermal agitations causing one end of the molecule (which appears to be flat on the surface at 298°K) to become desorbed, and provide additional sites for adsorption of other molecules.

The polyoxyethylene-containing surfactants are adsorbed to a lesser extent at higher temperatures than at lower ones. This may be due to an altered conformation of the PEG chain, or to an alteration of hydration.

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