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SURFACTANT INTERACTIONS WITH BIOMEMBRANES AND DRUG ABSORPTION

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Abstract This article summarises work which has been carried out at Strathclyde and elsewhere on the mechanisms of the effect of nonionic surfactants on drug absorption. Experiments carried out in whole animals are often difficult to interpret unless treatment is confined to a small or localised part of the animal e.g. the rectal cavity, because of dilution of the surfactant-drug system and possible interactions of components of the formulation with naturally occurring materials. Resort to simple animal models is essential if surfactant structure-activity relationships are to be obtained. Experiments on drug transport across the gill membrane of the goldfish, Carassius auratus and the isolated rabbit gastric mucosa are discussed in relation to the factors influencing increases in drug penetration. Concentration-dependent effects are discussed and some recent results on enhanced high dose methotrexate absorption in mice are discussed. Consideration is given to the biological effects of surfactants which can influence drug absorption from the gastro-intestinal tract of animals and human subjects and to the possibility that surfactants may be used deliberately not only to enhance drug absorption, but also to secure penetration into specialised tissues.

Drugs are almost never administered as such to the body, but as formulations containing many ingredients presumed to be inert. Surfactants used as emulsifying agents, solubilizers, suspensions stabilizers or as wetting agents in formulations can not be considered to be inert additives as they can lead to significant changes in the biological activity of the active agents in the formulation.

Utilisation of a drug involves its release from the formulation, its solution in the body fluids, and its passage through barrier membranes into the systemic blood stream before transport into tissues and eventual arrival at the target organ. Release of poorly soluble drugs from tablets and capsules for oral use may be increased by the presence of surfactants, which may decrease the aggregation of the drug particles and therefore increase the area of particle available for dissolution. The lowering of surface tension may also be a factor in aiding the penetration of water into the drug mass; this wetting effect is operative at low concentrations. Above the critical micelle concentration (CMC) the increase in the saturation solubility of the drug substance by solubilisation in the surfactant micelles can result in more rapid rates of drug solution. Where dissolution is the rate-limiting step in the absorption process, as it is with many poorly soluble drugs, an increase in rate of solution will increase the rate of drug entry into the blood and may affect peak blood levels. Very high concentrations of surfactant in excess of that required to solubilize the drug can decrease drug absorbption by decreasing the chemical potential of the drug.

The various sites at which surfactants may influence absorption are depicted in Fig.1.

Some surfactants have a direct physiological activity of their own and in the intact animal can thus affect the physiological environment e.g. by altering gastric residence time such that without physico-chemical intervention, a surfactant effect may be seen. It is only possible to isolate some of these effects and to examine the effect of surfactants in each. Studies in whole animals have sometimes given what appear to be contradictory results.

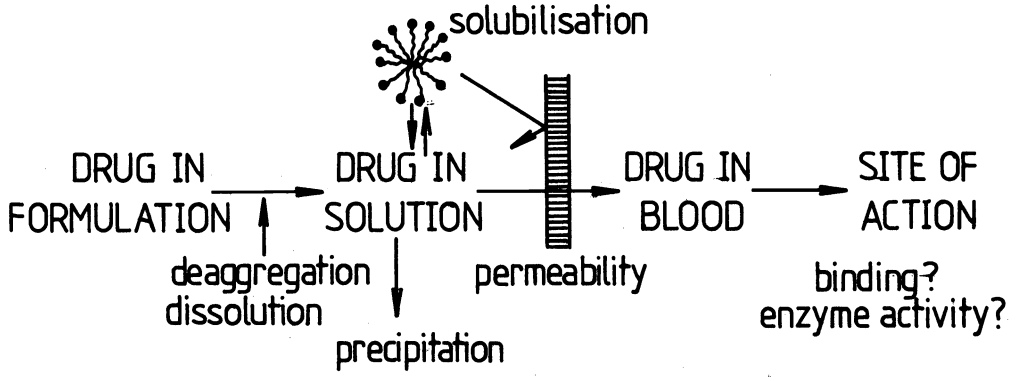

Fig. 1. Possible sites of surfactant influence on drug absorption and activity. Surfactants can affect deaggregation and dissolution processes, precipitation of systems, enhance membrane permeability and perhaps have an influence on drug metabolising enzymes or binding of drugs to receptor proteins.

Numerous studies on the influence of surfactants on drug absorption have shown them to be capable of increasing, decreasing, or exerting no effect on the transfer of drugs across biological membranes. (Ref. 1). Perhaps the earliest report of the effect of a surface-active agent on drug activity is that of Billard and Dieulafe (2), who noted that the toxic effect of curare injected intraperitoneally into guinea-pigs could be increased by the addition of low concentrations of soap and decreased by high concentrations. This biphasic action of surfactants has been noted many times since, but nonetheless the literature tends to be confused. The observed influence of surfactants depends on the concentration of the surface-active agent present in vivo (which is difficult to assess and which continually varies when the formulation has been administered to man or intact animal due to the surfactant absorption, distribution and metabolism.) Much of the confusion in the literature on this subject arises from discussion of the influence of different concentrations of a variety of surfactants and from attempts to generalise on the action of these varied surfactants on many different types of biological membrane.

EFFECTS OF SURFACTANTS ON MEMBRANE PERMEABILITY

This paper discusses some of the work we have carried out at Strathclyde on the factors affecting the transport of drugs in the presence of nonionic surfactants, in attempts at elucidating the structural features of the surfactants which allows them to be effective in altering membrane permeability. For an account of the literature on the subject up to 1968 the reader is referred to Ref.1, and for recent reviews of the topic to Refs. 3 and 4. Effects of surfactants on drug dissolution and release from dosage forms will not be treated here.

Interaction of nonionic surfactants with biological membranes

The disruption of membrane integrity and function by surface active compounds is at the centre of many of the observed biological effects of surfactants. Many surfactants have been studied to quantify their usefulness as solubilizing agents for membrane components for subsequent biochemical study. Nonionic surfactants have been most widely used as "chemically mild and efficient chaotropic agents" (Ref.5). Steps in the solubilization of the components of biological membranes by a nonionic surfactant are shown in Fig. 2. The ratio of surfactant to lipid is important in determining the exact nature of the interaction between amphipaths and membranes (Ref. 7) and the nature of the biological membrane is also important. A study (Ref.8) of the solubilization of mitochondrial inner membrane, microsomal and erythrocyte membrane components by Triton X-100, sodium dodecyl sulphate and sodium deoxycholate has shown considerable differences between these surfactants in their ability to solubilise protein and lipid phosphorus from the

mitrochondrial inner membrane, probably because of the high protein/lipid ratio in this membrane.

Human erythrocyte ghosts contain a relatively high proportion of cholesterol. Loizaga et al., (8) find surfactant/protein ratios more reliable than surfactant/lipid ratios in assessing the extent of membrane solubilization, and these workers suggest that the systematic use of this parameter would make data from different laboratories more readily comparable. Chemical and ultrastructural studies suggest that the first step in the membrane solubilization process (Ref.9) involves, at surfactant concentrations up to 0.1%, solution of the protein constituents associated with membrane structure. In the next stage (0.1-0.5% surfactant) lipids are solubilized after liberation from lipoprotein complexes. Selective solubilization of components is possible with some surfactants and membranes. Other sequences have been suggested which probably are, in fact, the same as those depicted in Fig. 2. The results of Foster and co-workers'(10) study of the action of nonionic detergent on a kidney membrane fraction suggest that membrane disruption involves binding of detergent monomers to exposed polar segments of membrane protein followed by the formation of co-micelles of the surfactant with segments of the membrane. Interactions below the surfactant CMC are evident and change only in magnitude at the CMC (Ref.10).

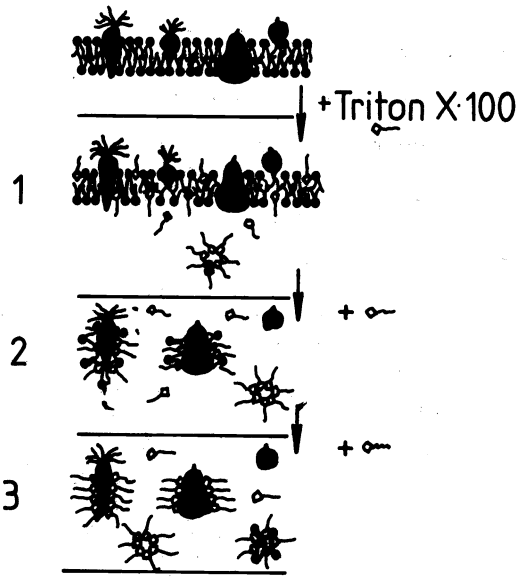

Fig. 2. Solubilization of the biological membranes by nonionic surfactants. The membrane model is taken from Ref.6. Depending on the ratio of surfactant/membrane lipids, different steps of solubilization may be obtained. In step 1, when a small amount of surfactant is present, the molecules of detergent are incorporated into the membrane without breaking it. In step 2, the membrane is solubilized into micellar solution containing mixed protein-lipid surfactant micelles in equilibrium with surfactant micelles and free surfactant molecules. Finally (step 3) when enough surfactant is added pure protein-surfactant micelles may be obtained in equilibrium with surfactant lipid and surfactant micelles.

after T. Gulik-Kraywicki, Biochim.Biophys. Acta, 415, 1- (1975)

Kirkpatrick et al., (11) measured the percentage solubilization of protein, lipid, cholesterol and sphingomyelin in the presence of Triton X-100; the results indicated significant protein solubilization below the CMC which is around 1mmol l^{-1}. Significant solubilization of cholesterol and sphingomyelin occurs only in the presence of 5mmol l^{-1}, leading Kirkpatrick et al., to propose that extensive binding of the nonionic surfactant occurs and that

this leads to a rise in the observed CMC to five times its normal value, in the absence of such binding.

Such interactions are directly relevant to the effect of surfactants on drug absorption. It has been found, for example, that there is some relationship between the absorption of salicylate or L-valine across rat jejunal tissue and release of protein and phospholipid induced by a series of nonionic surfactants (Ref.12).

Experiments with Carassius auratus

In choosing the common goldfish, Carassius auratus, as a model system for investigating the effects of surfactants and other additives on drug transport Levy and co-workers (13) noted that most of studies of surfactant effects, having been carried out on microbial systems, were inapplicable to multicellular organisms, as these can maintain homeostasis. In addition the presence of enzymes and other cell constituents in the cell membrane make unimicellar organisms particularly sensitive to the effects of surfactants. The major advantages of the fish system is that large quantities of test solution can be used, permitting the maintenance of constant concentration gradients across the membranes, which behave, as far as passive diffusion characteristics are concerned, in a similar way to human membranes.

Levy et al., (13) showed clearly an increase in absorption of sodium secobarbitone in the presence of low concentrations of polysorbate 80 at pH 5.9 and a decrease in activity through slower absorption at surfactant concentrations well above the CMC. Similar biphasic responses were observed by Florence and Gillan (14) when studying the absorption of thioridazine in the presence of nonionic surfactants. It was clear from these results that not all nonionic surfactants enhanced the absorption of the drug, some producing only a reduction in absorption above their CMC values. The group of surfactants used in this work did not form a convenient series although certain conclusions could be drawn from the results. Molecular size and hydrophilicity of the surfactant correlated roughly with effect: very hydrophilic surfactants are insufficiently surface active to display a significant effect on membrane permeability. Surfactants with large cross-sectional areas were thought to be unlikely to be able to penetrate the membrane lipid or to disrupt membrane protein-lipid bonds to bring about the increase in fluidity and permeability that is required for increased drug transport. In later experiments with nonionic surfactants of the Brij class (alkyl polyoxyethylene alkyl ethers with lauryl, stearyl or oleyl hydrocarbon chains) significant increases in the absorption of several barbiturates were noted (Ref.15) but correlation between effect and hydrophile-lipophile balance, for example, was difficult to establish. When subgroups of surfactants were considered, however, some patterns did emerge. Fig.3 shows the effect of HLB on absorption of phenobarbitone and thiopentone by goldfish. These results indicate some optimum HLB at which the enhancement of absorption is at a maximum. These trends are even clearer when surfactants with a given hydrophobe are compared. Fig. 4 shows the effect of a series of polyoxyethylene cetyl ethers ($C_{16}E_x$) on secobarbitone absorption by goldfish; results are plotted as a function of polyoxyethylene chain length. The maximum effect is exerted by the surfactant $C_{16}E_{14}$ which has an HLB of 14.4.

Comparison of Figs. 3 and 4 will show that the drugs studied are affected to different extents by a given surfactant. At 0.1% surfactant levels some solubilization of the barbiturate will be taking place and this will be different for the three drugs in question. Measurements are currently underway to quantify the interaction to eliminate the differences which might be due to differences in the degree of solubilization of drug in the system. One complication in the use of goldfish is the intrinsic biological activity of some of the surfactants manifested in concentration-dependent over-turn times (Ref.16), which are probably a reflection of the anaesthetic activity following absorption. Such problems are unlikely to be encountered in the use of isolated membranes especially when direct measurements of solute flux are made.

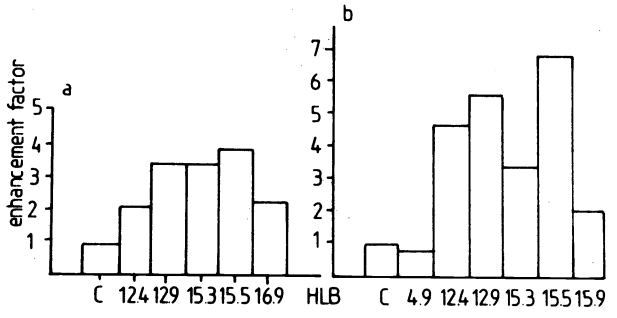

Fig.3. The influence of 0.1% nonionic (Brij) surfactants on the absorption of a) 0.1% phenobarbitone and b) 0.1% thiopentone by goldfish (n=5) as a function of surfactant HLB. Increase in absorption is plotted as an enhancement factor which is the ratio of reciprocal overturn time in water to that in the surfactant mixture. (Ref.15).

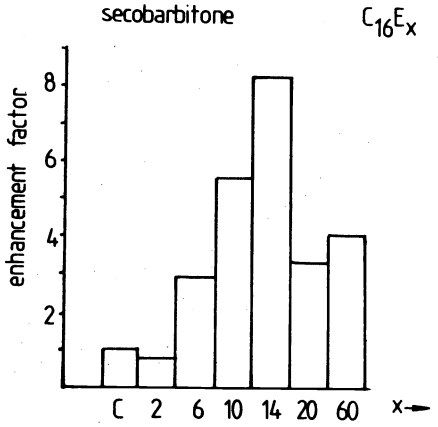

Fig. 4. The effect of nonionic surfactants, of general structure $C_{16}E_x$, on the absorption of 0.1% secobarbitone by goldfish (n=5) as a function of x, the polyoxyethylene chain length. (Ref.15).

Experiments with rabbit isolated gastric mucosa

In these experiments the active marker compound, paraquat, has no affinity for the surfactant micelles, thus the concentration dependency of action was not complicated by solubilization of the active species. The same range of surfactants was used as in the experiments with the fish. The isolated gastric mucosa was set up in diffusion chambers exposing 1.77 cm^2 of surface to the solutions (Ref.17). The change in permeability constant, K_p, on surfactant addition is shown in Figs. 5 and 6. Of the cetyl polyoxyethylene studied, $C_{16}E_{14}$ induces maximal values of K_p.

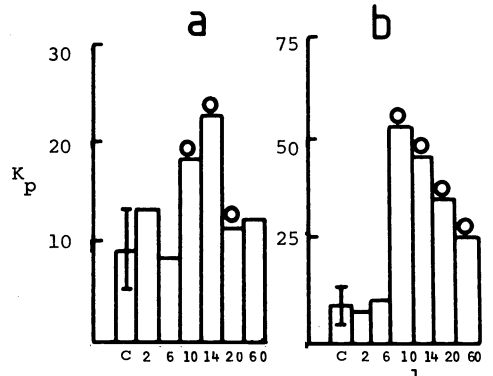

Fig. 5. Values of K_p for paraquat (cm h^{-1} x 10^3) obtained at a) 0.01% surfactant levels and b) at 1.0% surfactant levels with the isolated rabbit gastric mucosa. Results are plotted as a function of the ethylene oxide chain length of the $C_{16}E_x$ surfactants. C is the control (paraquat without additives). Results which are statistically different from the control values ($P < 0.05$) are marked with circles, from Ref.17.

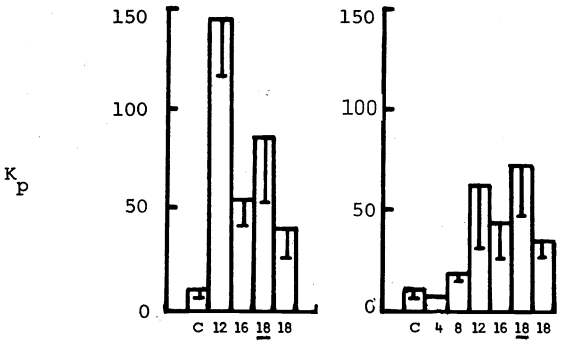

Fig. 6. The effect of 1% nonionic surfactant on values of K_p for paraquat (cm h^{-1} x 10^3) obtained with isolated rabbit gastric mucosa as a function of the alkyl chain length of a) surfactants with 10 ethylene oxide units and b) surfactants with 20 ethylene oxide units. The chain length is marked on the absissa. (Ref.17). 18 = oleyl

Even at concentrations as low as 1 x 10^{-3}% several surfactants in the series studied by us caused a significant increase in the rate of paraquat transport. Maximum effects are caused in the cetyl ether series by $C_{16}E_{10}$ at higher concentrations and $C_{16}E_{14}$ at lower concentrations. Maintaining the hydrophilic chain constant as in Fig.6, it can be seen that of the surfactants with a saturated hydrocarbon chain the C_{12} derivatives induce the greatest increase in permeability. The oleyl surfactants seem to have an effectiveness greater than anticipated from the hydrophobic chain length. Such influences explain why the simple parameter of HLB cannot cope with the subtleties of these effects, as HLB is relatively insensitive to unsaturation, and of course cannot detect differences in surfactant shape, especially as molecules of quite different size and physical properties can have the same HLB number, as for example C_6E_6 and $C_{12}E_{12}$.

The lauryl chain which appears to have distinctive properties in terms of membrane penetration and alteration in membrane permeability has been singled out in other studies. We have observed a clear maximum at C_{12} of intrinsic biological activity in a series of alkyl polyoxyethylene ethers (Fig. 7).

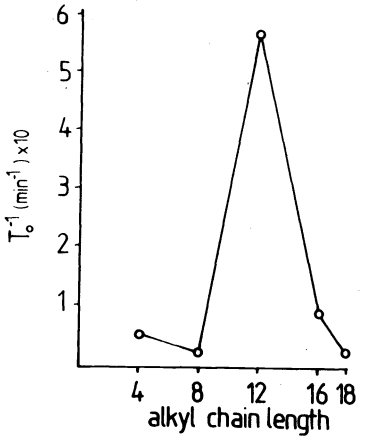

Fig. 7. Dependence of turnover time (1/T) of goldfish on surfactant alkyl chain length (C_xE_{10}).

Schott (18) has suggested that the particular effectiveness of the lauryl surfactants is due to the balance of two properties. As the homologous series is ascended the lipophilicity of the compounds increases, but the CMC decreases, thus limiting the concentration of monomers which can exist in the aqueous phase in the case of higher members of the series. From C_8 to C_{12} as the partition coefficient increases there is an increased opportunity for the surfactants to enter the biophase, whereas from C_{12} to C_{18}, while the thermodynamic tendency to partition into non-aqueous environments increases the decreasing concentration of monomers the surfactants may produce only a lower response. From work quoted earlier (Ref.11) adsorption of surfactant onto the high surface areas of membrane components can also influence behaviour. Some workers have suggested that the lauryl chain is of intrinsic biological importance in relation to its ability to disrupt lipid bilayers, having the optimal physical properties of lipophilicity and size, but as C_{12} compounds are also maximally irritant to the skin (Ref.19) where simple membranes are probably not involved, other factors are no doubt implicated. Dominguez et al., (20) have considered Schott's approach to the biological uniqueness of the dodecyl chain, but have postulated that its properties of skin penetration are related to the conformation of the chain, especially when adsorbed to or interacting with protein. Dominquez et al., postulate that by adopting a compact configuration the dodecyl chain can migrate deeper into skin structure and thereby be more active than more lipophilic compounds. This is very speculative and requires more experimental and theoretical study.

Schott's arguments should apply to a homologous series in which the hydrophilic chain length alters too. A semi-quantitative examination of the situation is made in Fig. 8. Here the experimentally determined (Ref.17) CMC's of the surfactant are used with idealised diagrams of monomer concentration as a function of total surfactant concentration. When measurements of surfactant action are made at 0.01% concentration levels, the monomer concentrations are as shown. If it is assumed that the monomer is the active species, a maximum in activity is readily shown by choice of partition coefficients such as those shown for members of the homologous series. This approach will only obtain at concentrations close to the CMC's because of the ability of the surfactant to solubilize membrane components and to disrupt membrane structure at concentrations in excess of the CMC. It seems likely that at low concentrations the low activity of the hydrophobic members of the series is limited by micellisation, and in the case of $C_{16}E_2$, by insolubility.

It could well be that many of the results of increased transport rates are determined by membrane damage, rather than by reversible physical effects; studies on the solubilization of protein, cholesterol and phospholipid from microsomal membranes (Ref.21) with surfactants of the same class seem to support this view as they show that maximal effects are obtained with $C_{16}E_{10}$ present at a level of 1.3mM. At high concentrations of surfactant one

might therefore anticipate that as the mechanism of action has shifted from membrane penetration and labilisation to solubilisation of membrane components, that the effect on membrane permeability would seem to fall as the ethylene oxide chain was increased. This could be the interpretation of the results in Fig. 5b, but the marked difference between $C_{16}E_6$ and $C_{16}E_{10}$ would require explanation.

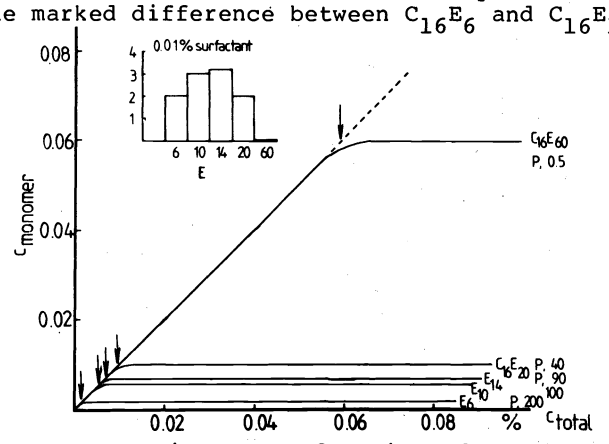

Fig.8. Monomer concentrations as a function of total surfactant ($C_{16}E_x$) concentration. Experimental CMC's are marked by arrows. At 0.01% total surfactant levels, the monomer concentrations will be approximately given by the CMC values except for $C_{16}E_{60}$ whose CMC is 0.06%. Inset shows absorption profile if values of partition coefficient (P) shown apply.

In vivo experiments

None of the above is of any use if when applied in vivo surfactants are unable to enhance the absorption of drugs. However, the evidence that nonionic surfactants can increase absorption is clear-cut in some instances Absorption of normally nonabsorbed or poorly absorbed water soluble drugs from a Thomas gastric fundic pouch of the dog is greatly increased by certain surfactants (Ref.22). Vitamin B_{12} absorption from both stomach and intact GI tract of the rat is similarly enhanced (Ref.23). As might be anticipated, while blood levels of cephaloridine are elevated several fold when nonionic surfactant is added to the ligated stomach, the influence of the surfactant in the intact GI tract is diminished and confined to the first 30 minutes, after which approximately normal levels of drug are observed (Ref.24). Kreutler and Davis (24) commenting on their results conclude that the absorption promoters exert their rapid and transient effect in the duodenum and small intestine and exert little effect in the stomach: "This may be due to rapid emptying of the stomach followed by dilution of the dose in the duodenum, or to the subsequent rapid passage of a liquid dose out of the more absorptive upper part of the small intestine. The comparatively poor results in the intact animals also raise the interesting question of possible specific incompatabilties of polyoxyethylene-20-oleyl ether with intestinal secretions in the intact GI tract".

Recently insulin absorption via the jejunum has been effected by administration of insulin-cetomacrogol solutions to diabetic rats (Ref.25). As insulin administered ½ hr after cetomacrogol elicited a hypoglycaemic effect the results are most likely due to a membrane effect rather than surfactant - prevention of insulin degradation. There have been successful attempts to achieve insulin absorption per rectum (Refs.26-28). Nonionic ethers, anionic, cationic and amphoteric surfactants, as well as bile acids, increased absorption. The optimal effect with nonionic surfactants was obtained with $C_{12}E_9$ (1%) (Ref.27), the effect of both polyoxyethylene chain lengh and alkyl chain having been determined (Table 1).

We have recently studied the effect of polysorbate 80 on the absorption of methotrexate (MTX) from oral preparations in mice and in human subjects (Ref.29). MTX is absorbed erratically and incompletely from oral doses beyond 30mg m^{-2} , a saturable mechanism of transport operates, probably an active transport process of low capacity characteristics. Some results are shown in Table 2 for low dose (0.5mg kg^{-1}) and high dose (3mg kg^{-1}) MTX preparations.

* Table 1. Effects of polyoxyethylene (P.O.E.) (n) fatty alcohol ethers in insulin suppositories* on blood glucose level in rabbits.

Surfactant in suppository	Decrease in blood glucose %			
	30	60	90	120(min)
$C_{12}E_3$	-8.8±7.7	-3.0±3.5	-11.2±2.3	-9.8±4.6
$C_{12}E_6$	-12.3±0.6	-23.8±6.9	-20.6±6.5	-11.2±6.1
$C_{12}E_9$	-12.7±8.5	-47.9±5.6	-47.1±7.4	-32.6±11.2
$C_{12}E_{25}$	+0.6±1.2	-4.2±2.6	-4.0±2.8	-0.9±1.0
$C_{12}E_{40}$	+17.3±2.9	+18.5±2.5	+14.9±3.1	+13.5±8.2
C_8E_9	+3.9±5.5	+12.8±8.0	+13.6±9.2	+13.0±6.2
$C_{10}E_9$	-21.6±4.8	-36.2±3.7	-16.2±5.1	-12.6±6.8
$C_{16}E_9$	-28.4±3.6	-43.1±2.6	-35.9±5.7	-16.8±5.4
$C_{18}E_9$	-22.0±6.2	-22.2±3.2	-19.9±4.8	-26.2±7.9

from Ref.28.

* Insulin suppositories contained 0.5% polyoxyethylene fatty alcohol ethers and 1 U kg^{-1} of insulin in corn oil. The initial blood glucose concentration was 118.3 ± 6.2mg/100 ml. Each value represents the blood glucose concentration at 30,60,90 and 120 min after rectal administration of insulin suppositories and mean of 3 rabbits ± s.e.m.

Table 2. Serum concentrations of MTX in the presence and absence of polysorbate 80.

Dose of MTX	0.5 mg kg^{-1}				3 mg kg^{-1}			
% polysorbate 80 in MTX preparation:	nil	0.1	2	6	nil	0.1	2	6
Maximum MTX concentration in serum (umol l^{-1})	0.2	0.22	0.22	0.6	0.32	0.32	0.41	0.51

from Ref.30.

Although there was no significant effect of surfactant on MTX levels in serum at dosages of 0.5mg kg^{-1}, except at the highest concentration of polysorbate,there is an increase of MTX uptake at a dosage of 3mg kg^{-1} in the presence of 2% and 6% polysorbate 80. 3mg kg^{-1} MTX has been administered p.o. to mice as a solution with or without 6% polysorbate 80 and as a freshly prepared multiple w/o/w emulsion (containing a total of 0.25% polysorbate 80 and 3.25% Span 80) (see Fig.9.). There are significantly higher serum levels of MTX in mice given 3mg kg^{-1} MTX with 6% polysorbate 80 at 30, 45 and 60 minutes after administration and in mice given the w/o/w multiple emulsion at 15, 120 and 240 minutes compared to the mice given 3mg kg^{-1} MTX alone, [$p < (0.0025)$, (0.05), (0.025) and $p < (0.05)$, (0.0125), (0.0125) respectively]. These results suggest that polysorbate 80 and other nonionic surfactants formulated into suitable oral dosage forms might be of use in improving the bioavailability of high oral dose MTX from the gastro-intestinal tract, opening up the possibilities of wider

use of oral MTX clinically. This hypothesis is now being tested in patients. Lack of effect of the surfactant at low doses again suggests that active transport processes are unaffected by surfactant, but that passive transport at high doses is facilitated. In human subjects one cannot carry out the experiments required to obtain surfactant structure-action relationships, partly because of the unknown toxicity of many surfactants and partly because of the impossibility of assembling sufficient data, especially when dealing with a drug such as MTX which cannot be used in volunteers.

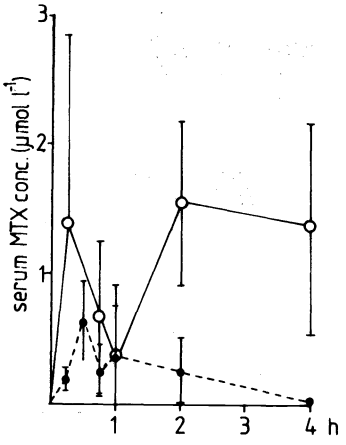

Fig. 9. Absorption of 3mg kg^{-1} methotrexate from the gastro-intestinal tract of NMR mice. Dotted line: methotrexate solution in water. Solid line is multiple w/o/w emulsion containing 0.25% polysorbate 80 and 3.25% Span 80. (Ref. 29)

Increase in drug absorption without a consequent change in distribution of the drug, for example penetration of MTX and other anti-cancer agents into tumour sites, is a relatively minor advantage. We have, however, preliminary evidence that high dose polysorbate increases the levels of MTX in brain.

Some generalisations

Surveys of the literature on the subject of surfactant effects on drug absorption do not readily allow generalisations to be made, even if one restricts one's attention to nonionic surfactants. Neglect of the nature of the drug concerned is inadmissable, as surfactant-drug interactions might be of paramount importance in determining the resultant effect of the surfactant. One can disern in the experiments with goldfish, for example, some general trends which lead to a suggestion that the concentration -dependence of surfactant effects can take the forms outlined in Fig.10, which are determined to some extent by interaction or lack of interaction of drugs with surfactant in the post CMC region.

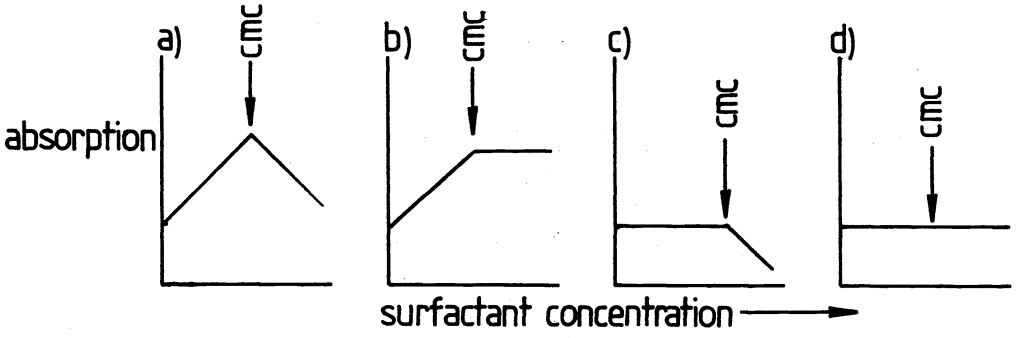

Fig. 10. Four possible profiles of surfactant induced effects of drug absorption as a function of surfactant concentration.

Typical of many systems is that shown in Fig. 10a where absorption is increased up to the CMC but reaches a maximum at the CMC through solubilisation of the solute drug in the micellar phase. In Fig. 10b the behaviour of a surfactant which increases permeability but has no affinity for the drug is shown. Fig. 10c is a profile that would be obtained from a surfactant which solubilised drug above the CMC but had no effect on membrane permeability; Fig. 10d shows the null effect of a surfactant which neither affects membrane permeability nor solubilizes drug. Added to these would be the various profiles obtained by other homologous surfactants, as discussed above,making the job of prediction of surfactant effects somewhat difficult.

I have ignored in this account the physical effects of surfactant on dosage form, which can be significant, and have also neglected those biological effects of surfactants on gastrointestinal function which can obtrude on the physical effects, perhaps overriding them. The object here has been to show that some but by no means all nonionic surfactants can enhance transport of drugs across biomembranes. The effect depends on both surfactant structure and the nature of the drug; some progress has been made with understanding the former, but more work is required on the latter. Properly designed formulations containing surfactants which can maintain drug in solution following oral administration, or decrease the onset of precipitation of a poorly soluble drug (such as MTX) might enhance absorption because of the maintenance of a high level of saturation of the system. Rarely will a single mechanism operate in isolation.

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