value for the short length (25 cm) catheter was lower than for the polyurethane catheters, but the standard deviation was higher.

Of all catheters tested the polyethylene catheter showed the lowest drug sorption: only $0{\cdot}2 \pm 0{\cdot}1\%$ (mean $\pm$ s.d.) of the amount of ISDN administered was sorbed. The sorption to the silicone catheter was $6{\cdot}1 \pm 0{\cdot}8\%$ and was similar to values observed for polyurethane catheters with a similar Shore hardness.

For all catheters a similar sorption profile was observed. During the first 10 min a sharp decrease in the amount of ISDN available was seen, probably caused by adsorption of the ISDN to the catheter wall. Afterwards, the amount of ISDN available increases towards the original level.

In conclusion, the sorption of ISDN to central venous catheters is low compared with the sorption observed for polyvinylchloride tubings. Polyethylene catheters showed the lowest sorption followed by the polyvinylchloride thermodilution catheter. Within the cycloaliphatic polyurethanes an inverse relation between Shore hardness and sorption was observed.

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# A comparison of the incorporation of model steroids into non-ionic micellar and microemulsion systems

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**Abstract**—The incorporation of testosterone and two of its esters, and progesterone and one of its esters (log $P_{oct}$ varying from 3·3 to 6·9) into 2% w/w soybean oil/Brij 96 microemulsions and Brij 96 surfactant systems has been examined. Possible sites of incorporation have been investigated. The drug carrying improvement of an oil-in-water microemulsion over a micellar system appears to depend on the solubility of the drug in the dispersed oil phase and is significant only for very lipophilic drugs.

Non-ionic oil-in-water (o/w) microemulsions represent an interesting prospect for the development of formulations suitable for the incorporation of poorly water soluble drugs. Such systems are transparent, easy to prepare, thermodynamically stable and may be sterilized by filtration.

It has previously been suggested that unless the drug has significant solubility in the dispersed oil phase, the increase in drug loading in these systems, compared with a micellar solution will be small (Malcolmson & Lawrence 1990).

In this study we report on the level of incorporation of five poorly water soluble, structurally related steroids, of varying log $P_{oct}$ in surfactant systems of the non-ionic surfactant Brij 96, and 3-component o/w microemulsions produced from Brij 96 and containing 2% w/w soybean oil.

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## Materials and methods

*Materials.* All chemicals were used as received. Testosterone, testosterone propionate, testosterone enanthate, soybean oil, 1-octadecene, polyoxyethylene-10-oleyl ether (Brij 96) and dimethoxytetraethylene glycol (DMTG) were obtained from Sigma Chemical Co. (Poole, UK). Methanol (HPLC grade) was obtained from FSA Laboratory Supplies (Loughborough, UK). Progesterone was a gift from Cox Pharmaceuticals (Barnstaple, UK) and medroxyprogesterone acetate a gift from Upjohn Ltd (Crawley, UK). Triple-distilled water, obtained from a well-seasoned all-glass still, was used throughout.

*Sample preparation.* The microemulsions and surfactant solutions were prepared by adding the required weight of each ingredient, heating to 343 K for 5 min and returning to room temperature (294 K), with constant stirring. The area of existence of 3-component o/w microemulsion systems composed of soybean oil, Brij 96 and water, which remain stable at ambient conditions for at least one month, was determined by producing a large number of individual samples. Oil-in-water microemulsions consisting of 2% w/w soybean oil and either 10, 15 or 20% w/w Brij 96 (testosterone, testosterone proprionate and testosterone enanthate) or 15 or 20% w/w Brij 96 (progesterone and medroxyprogesterone) were used to test drug incorporation compared with micellar solution or equivalent Brij concentration.

*Drug incorporation.* The levels of incorporation of each drug were determined by introducing a known excess of drug to

duplicate samples of each micellar and microemulsion preparation. Solubility of the five drugs in triple-distilled water, soybean oil, 1-octadecene, and varying concentrations of DMTG in water, were also determined. The samples were equilibrated in a shaking water bath at 298 ± 1 K. After 8 days the excess drug was separated from the water, micellar and microemulsion samples by filtration through a 0·22 μm Millipore cellulose acetate/nitrate filter. Excess drug was removed from soybean oil, 1-octadecene and the DMTG/water mixtures by centrifugation. The concentration of drug in the resulting clear preparations was determined using a Perkin Elmer Lambda 5 UV spectrophotometer after appropriate dilution with methanol.

**Results and discussion**

The area of microemulsion existence is represented by the shaded region of the partial triangular diagram drawn in Fig. 1. From this information, compositions containing 2% w/w soybean oil were selected for drug incorporation studies. This fairly low oil content was chosen, firstly in order to ensure samples were well within the o/w microemulsion area, and secondly to allow a comparison with surfactant systems containing a wide range of surfactant concentrations. The addition of the drugs did not appear to affect the stability of the microemulsion systems investigated; all samples tested remained as clear liquids in equilibrium with excess drug.

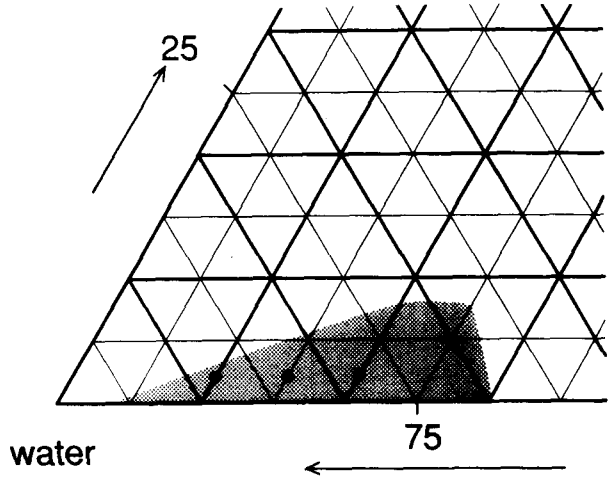


FIG. 1. Partial triangular diagram showing area of existence (shaded) of o/w microemulsion systems for soybean oil/Brij 96/water systems.

The drug uptake in micellar solutions and 2% w/w soybean oil microemulsions for the steroids are given in Table 1. In all cases drug incorporation increases with increasing surfactant content. At the same concentration of surfactant, there is no significant difference ($P > 0.05$) between the uptake of progesterone (at 20% Brij levels) and testosterone and medroxyprogesterone (at all levels tested) into the microemulsion systems compared with that of a micellar preparation. There is, however, a significant increase over the micellar solutions in the amount of testosterone propionate, testosterone enanthate and progesterone (at 15% Brij 96 concentration) found in the microemulsion systems. The increase in solubilization in the microemulsion systems compared with the micelles was greatest at low surfactant concentrations.

To explain these results, the possible sites of drug incorporation into the surfactant systems were considered. The drugs studied were all poorly water soluble (see Table 2) hence the amount dissolved in the external aqueous phase will be small. Consequently, most drug incorporation is expected within the micelle or microemulsion droplets. However, the micelle and microemulsion droplets may themselves be divided into regions of varying polarity. The non-ionic micelles formed by Brij 96 would be expected to consist of a liquid hydrocarbon core surrounded by a mantle of polyoxyethylene chains. In the region closest to the core, the mantle is most likely to consist of pure polyoxyethylene oxide. As the distance from the core increases so too does the hydration of the polyoxyethylene chains (Elworthy & Patel 1982). In a microemulsion droplet, soybean oil is also present. Due to the size of the triglyceride molecules present, soybean oil is not expected to penetrate into the surfactant hydrogen chains (Alander & Warnheim 1989); therefore it is assumed that the central core of the o/w microemulsion droplet will consist exclusively of soybean oil. This soybean oil core may then be expected to be surrounded by the oleyl hydrocarbons of the surfactant molecule, and finally by a mantle of ethylene oxide chains, increasing in hydration as the distance from the core increases.

Table 2 gives the solubility of each drug in the soybean oil and 1-octadecene. It can be seen that solubility in both these hydrocarbon phases increases with increasing lipophilicity (indicated by log $P_{oct}$ (Craig 1990)). 1-Octadecene is a limited model chosen to represent the oleyl (9-octadecene) region which forms the central core of the micelle, and the hydrocarbon region immediately surrounding the soybean oil in the microemulsion droplets.

Table 1. Incorporation of test compounds into micelles and microemulsions.

| | | %w/v drug incorporation ±s.d. | |
|---|---|---|---|
| Drug | %w/w Brij 96 | Micellar system | Microemulsion |
| Testosterone | 10 | 0·172±0·015 | 0·223±0·025 |
| | 15 | 0·218±0·021 | 0·230±0·049 |
| | 20 | 0·306±0·024 | 0·297±0·015 |
| Testosterone propionate | 10 | 0·290±0·041 | 0·402±0·035* |
| | 15 | 0·351±0·072 | 0·531±0·056* |
| | 20 | 0·447±0·098 | 0·656±0·080* |
| Testosterone enanthate | 10 | 3·50±0·36 | 5·72±0·34* |
| | 15 | 4·56±0·43 | 5·89±0·43* |
| | 20 | 5·24±0·59 | 6·19±0·47* |
| Progesterone | 15 | 0·629±0·067 | 0·789±0·036* |
| | 20 | 0·906±0·19 | 0·911±0·038 |
| Medroxyprogesterone acetate | 15 | 0·511±0·075 | 0·544±0·053 |
| | 20 | 0·689±0·032 | 0·748±0·057 |

*Indicates a significant difference ($P < 0.05$) between uptake into the microemulsion and micellar systems at the same concentration of surfactant.

Table 2. Physicochemical properties and solubilities (%w/v) of the test compounds at 298 K.

| | Testosterone | Testosterone propionate | Testosterone enanthate | Progesterone | Medroxyprogesterone acetate |
|---|---|---|---|---|---|
| Mol. wt | 288·4 | 344·5 | 400·6 | 314·5 | 386·5 |
| log $P_{oct}$* | 3·35 | 4·78 | 6·90 | 3·85 | 4·27 |
| Mean solubility ± s.d. in: | | | | | |
| Water | 0·0041 ± 0·0006 | 0·0009 ± 0·0002 | 0·00017 ± 0·0004 | 0·00004 ± 0·0002 | < 0·00007 |
| Soybean oil | 0·601 ± 0·056 | 3·42 ± 0·29 | 31·5 ± 2·1 | 2·16 ± 0·19 | 0·43 ± 0·073 |
| DMTG | 4·4 ± 0·006 | 12·0 ± 0·14 | 91·2 ± 4·9 | 5·14 ± 0·41 | 1·32 ± 0·047 |
| 1-Octadecene | 0·040 ± 0·009 | 1·51 ± 0·013 | 57·8 ± 3·3 | 0·455 ± 0·009 | 0·042 ± 0·002 |

*From Craig (1990). Calculated using *CLOGP* version 3.54.

The solubility of testosterone and its esters in DMTG/water mixtures was undertaken in an attempt to model drug solubility in the hydrated polyoxyethylene layer of the micelle or microemulsion droplet. Pure DMTG was chosen to represent the local environment of dehydrated polyoxyethylene (Patel et al 1981) closest to the hydrocarbon core. The lower DMTG concentrations represent increasing hydration of the polyoxyethylene as the distance from the core increases. All three drugs tested showed a significant increase in solubility with increasing DMTG as shown in the graph of log %w/w drug incorporated vs %w/w DMTG (Fig. 2). A similar trend has been previously seen for other poorly water soluble drugs (Elworthy & Lipscomb 1968; Groves et al 1984). At DMTG concentrations less than 80% w/w, testosterone is found to have the greatest solubility and testosterone enanthate the least. In the more dehydrated samples, however (< 20% w/w water), the solubility of the drugs in the mixtures increases with increasing log $P_{oct}$.

The combined results of all these solubility investigations indicate that with increasing lipophilicity (represented by log $P_{oct}$) increasing solubility of a drug is expected in the soybean oil core of an o/w microemulsion, in the region containing the hydrocarbon portion of the surfactant (which will constitute the core of a micelle and the outer hydrocarbon core of a microemulsion) and in the essentially dehydrated polyoxyethylene region closest to the core in both micelles and microemulsions.

The solubility results (Table 2) can be used to explain the difference in incorporation of the steroids. Considerably more testosterone enanthate would be expected in the dehydrated polyoxyethylene chains of the surfactant, and in the hydrocarbon core of a micelle or the dispersed oil/hydrocarbon core of a microemulsion. Hence much higher values of testosterone enanthate (highest log $P_{oct}$) incorporation were found in both these systems.

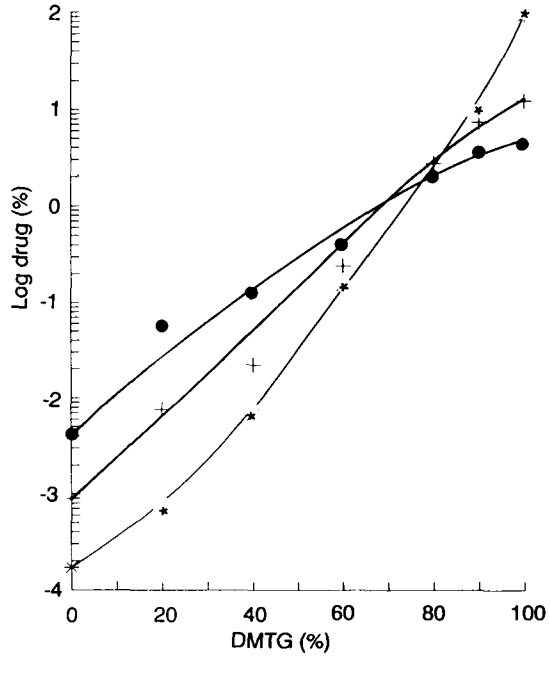


FIG. 2. Log %w/v drug incorporated vs %w/w DMTG. ● Testosterone, + testosterone propionate and * testosterone enanthate.

It appears that considerable solubility of the drug in the dispersed soybean oil phase is required in order for a microemulsion to exhibit significant improvement in its drug loading capabilities over a micellar solution of equivalent surfactant concentration. This is expected to be especially true with only a small amount of oil phase such as the 2% w/w soybean oil used here. Hence, the greatest improvement in drug incorporation is seen with testosterone enanthate, which has the largest log $P_{oct}$ and soybean oil solubility. It was, however, found that in those systems which exhibited an improvement in the drug carrying capacity, the increase was greater than that predicted based on the addition of the micellar solubilization plus the amount of drug that will dissolve in the 2% w/w soybean oil.

The results of this study suggest that the higher the solubility of a drug in the soybean oil the more likely that there will be a significant improvement in the drug-carrying capabilities of the microemulsion system over a micellar system of the same surfactant concentration. It would, therefore, appear that two important variables in using o/w microemulsions as a formulation alternative are the percentage of dispersed hydrophobic phase present and the solubility of the drug in that phase.

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