A simultaneous non-linear least squares fit with respect to the equations 4, 5 and 6 of the diazepam vs prazepam x_m experimental data, using a grid search method (Bevington 1969), may be carried out, giving w/RT = 2·2 and C/RT = 0·85 as the best fitting parameters. In Table 1, the calculated x_m values for prazepam starting from the diazepam data, and following the aforementioned procedure are also shown. The calculated solubilities fit the experimental data well within the experimental error margin.

This result may confirm, in a first approximation, that micellar solubilization data can agree with the simple model of non-ideality provided by the regular solutions approach. The procedure allows the prediction of the solubility of prazepam/diazepam in an n-alkyl-polyoxyethylene non-ionic surfactant aqueous solution, provided the solubility of one of them is known.

The moderately high positive value of the w parameter may be in accordance with a reputed high degree of inmiscibility between micellar and drug components, as the low solubility values obtained seem to indicate (Guggenheim 1967). The free energy transfer from the solid to the micellar phases of the cyclopropyl radical of prazepam, C = 2·1 kJ mol^{-1}, is also in the range of other established values (Tanford 1980).

The approach described suggests that micellar solutions may be amenable to analysis in terms of bulk thermodynamic concepts, and that generalizations of solubilization results in series of homologous surfactants and/or chemical compounds are possible.

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Preparation of single bilayer liposomes by an electrocapillary emulsification method

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The single bilayer liposomes have been prepared by an electrocapillary emulsification technique based on interfacial fluctuation in the absence of surfactant. Electron microscopy showed the liposome to be a unilamellar vesicle with a size generally in the range 60–120 nm.

Electrocapillary emulsification is based on interfacial tension between two phases in contact with each other when under the influence of a potential difference. When a potential difference higher than the critical voltage of emulsification is applied to an oil/water interface, the interfacial tension is reduced almost to zero and spontaneous emulsification occurs, due to the interfacial fluctuation, in the absence of surfactant or in the presence of a very small amount (Watanabe et al 1978).

The emulsions formed are monodisperse and stable, the average particle radius being less than 0·1 μm. Arakawa & Kondo (1980, 1981) reported that poly-(N^{α},N^{ε}-1-lysinediylterephthaloyl)(PPL) microcapsules containing sheep erythrocyte haemolysate were prepared by an interfacial polymerization technique using electrocapillary emulsification as the means of producing very fine haemolysate droplets for encapsulation.

Liposomes consist of concentric closed lipid bilayers alternating with aqueous compartments. The liposomal suspension forms liquid crystal dispersions, the droplets being very stable. We have developed a novel method for liposome production based on the electrocapillary technique.

Materials and method

Fig. 1 shows the schematic diagram of the apparatus for electrocapillary emulsification. The oil phase (dichloromethane, A) in the glass syringe (D) is injected into the aqueous phase (B) by means of an electrically driven

* Correspondence.

piston (P), which pushes the fluid through a needle (E). This needle also functions as an electrode. The potential difference between the needle electrode and the platinum electrode (C) is measured by the voltmeter (V). The container of the aqueous phase under N_2 atmosphere is surrounded by a water-bath (G) kept at 40 °C. The contents of the container are continuously stirred by a magnetic stirrer (H).

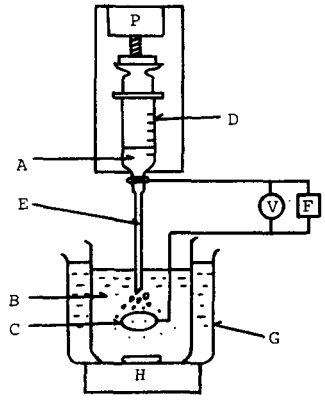

FIG. 1. Schematic diagram of the apparatus for electrocapillary emulsification. A, oil phase; B, aqueous phase; C, platinum wire; D, glass syringe; E, needle; F, direct current supply; G, water bath; H, magnetic stirrer; V, voltmeter; P, driven piston.

For the preparation of liposomes, the disperse phase in the container was used as the inner aqueous phase to be encapsulated within the liposomes. Therefore, the volume and the contents of the dispersed phase may be varied according to need. Dichloromethane containing the lipid mixture (phosphatidylcholine 100 μmol, cholesterol 50 μmol) was used as oil phase. This phase (2 ml), which was placed in a tube ending in a fine capillary, was introduced into the aqueous phase containing water soluble compounds (marker) (100 ml) and a high positive potential applied to the liquid. As the voltage was slowly increased, the droplets which issued from the capillary became elongated and formed a steady stream of threads. With increase in voltage, the threads became finer and finer and broke up into droplets. Ultimately, at a voltage above 400 V, a cloud of very fine droplets issued from the capillary, at a constant velocity of 0·1 ml min^{-1}. At this stage, lipid molecules were orientated on the surface of each droplet and then formed a stable bilayer membrane. In the final stage of process, the free (non-trapped) marker was filtered by a gel filtration method using Sephadex G-50 column (2·5 × 20 cm).

Fig. 2 shows electron micrographs of liposomes prepared by electrocapillary emulsification. The liposomes are seen to be unilamellar vesicles, mostly distributed in a narrow range of 60–120 nm.

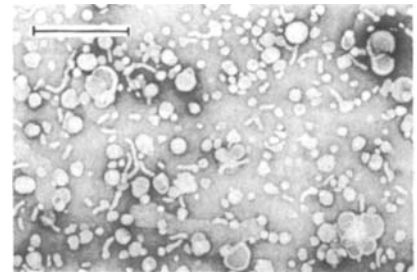

FIG. 2. A negative stain electron micrograph of liposomes prepared by electrocapillary emulsification. Bar indicator 500 nm.

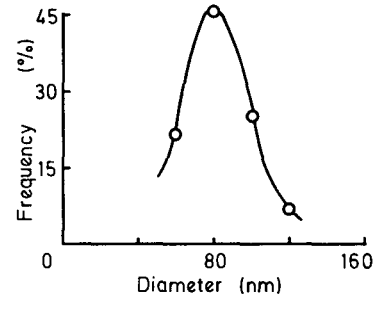

FIG. 3. Electron microscopy histogram for liposomes prepared by electrocapillary emulsification.

Particle size distribution curves calculated using the micrographs in Fig. 2 are shown in Fig. 3. A sharp size distribution with a peak at 80 nm was observed. The mean diameter and standard deviation of liposomes were 84 and 22 nm, respectively.

The electrocapillary emulsification method is ideally suitable for liposome formation and for the entrapment of many substances except enzymes. Furthermore, this technique is simple and less time-consuming compared with other methods.

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