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COMMUNICATIONS

The effect of temperature on the conductivity of gels and emulsions prepared from cetrimide and cetostearyl alcohol

R. C. ROWE*, H. K. PATEL, *ICI Pharmaceuticals Division, Alderley Park, Macclesfield, Cheshire SK10 2TG, UK*

The conductivity of gels and emulsions containing cetrimide, cetostearyl alcohol, liquid paraffin and water has been studied over the temperature range +35 to −10 °C. All samples froze at temperatures below −5 °C and exhibited hysteresis on rewarming to room temperature with an initial increase in conductivity up to 15 °C followed by a decrease to 25 °C. The amount of hysteresis was dependent on the cetostearyl alcohol content and appeared to be related to changes in the microstructure of the liquid crystalline network.

Conductivity measurements are routinely used in colloid science, e.g. as a method for assessing either the critical micelle concentration of a surfactant or the state of dispersion of an emulsion. Measurements as a function of temperature have recently been used to assess the thermal stability of pharmaceutical emulsions (Garti & Magdassi 1982). We have used conductivity measurements to follow the thermal stability both of gels and emulsions prepared using the mixed emulsifier system of cetrimide and cetostearyl alcohol.

Materials and methods

All the materials used were of Pharmacopoeial grade. The ternary gel systems T_1–T_6 were prepared according to the formulae in Table 1. Cetostearyl alcohol at 80 °C was dispersed in aqueous cetrimide solution at the same temperature and stirred gently with a paddle stirrer for a period of 1 h before being allowed to cool to approximately 60 °C. The mixture was then homogenized using a Silverson, multi-purpose, high speed mixer until the setting point of the gel was reached or for a period of not more than 15 min. The gel was then allowed to cool to room temperature (25 °C). The emulsion E_1 was prepared in a similar fashion except that the cetostearyl alcohol was dissolved in the liquid paraffin at 80 °C before being added to the aqueous cetrimide solution at the same temperature. All systems were allowed to stand for at least 2 weeks before being tested.

* Correspondence.

Conductivity measurements were made using a simple conductivity cell in the form of a probe (Griffin, PJK – 320-518Q) placed in a small sealed plastic container containing approximately 15 g of sample and coupled to an Autobalance Universal Bridge (B642, Wayne Kerr Ltd). The container was immersed in a water bath containing propylene glycol enabling measurements to be made over the temperature range −10 °C to +40 °C. Temperature measurements were made using a thermocouple attached to the conductivity probe.

Results and discussion

The effect of temperature cycling on the percentage change in conductivity (the initial room temperature 25 °C, readings are given in Table 1) for all the samples tested is shown in Figs 1 and 2. On cooling of the samples from 35 °C, their conductivity decreased linearly until they froze at −4·7 °C. At this point there was an instantaneous rise in temperature to 0 °C accompanied by a concurrent rise in conductivity. However, as the temperature of the water bath was maintained at −5 °C, both the temperature and conductivity of the samples fell until they reached steady state conditions. On heating there was no perceptible increase in conductivity until approximately −2 °C after which the increase was rapid as the samples thawed. The percentage increase in conductivity over the temperature range −2 to +2 °C was related to the cetostearyl alcohol concentration, being only 40% in the case of the

Table 1. Composition and specific conductivity of the ternary gels and emulsions used in this work (all concentration % w/w).

	T_1	T_2	T_3	T_4	T_5	T_6	E_1
Cetrimide	0·5	0·5	0·5	0·5	0·5	0·5	0·5
Cetostearyl alcohol	0·5	1·0	2·5	4·0	6·0	10·0	10·0
Liquid paraffin	—	—	—	—	—	—	20·0
Purified water to	100·0	100·0	100·0	100·0	100·0	100·0	100·0
Specific conductivity (μmho cm^{-1}) at 25 °C	286·5	67·2	53·9	33·4	30·4	17·5	12·9

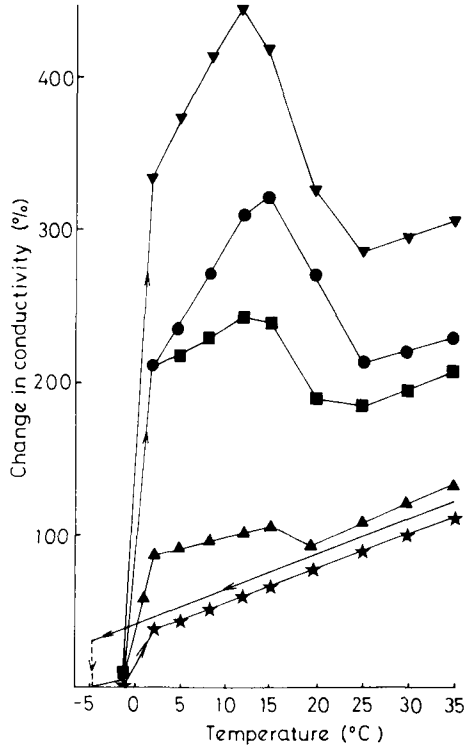


FIG. 1. The effect of temperature on the percentage change in conductivity of the ternary gels T_1–T_5 containing ★ 0·5%; ▲ 1%; ■ 2·5%; ● 4%; ▼ 6% w/w cetostearyl alcohol.

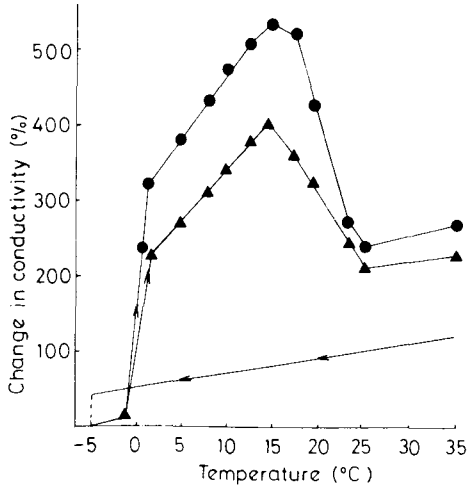


FIG. 2. The effect of temperature on the percentage change in conductivity of a ternary gel containing 10% w/w cetostearyl alcohol ●; and an emulsion containing 20% w/w liquid paraffin ▲.

ternary gel containing 0·5% cetostearyl alcohol to 360% in the case of the ternary gel containing 10% cetostearyl alcohol. After this temperature only the ternary gel containing 0·5% cetostearyl alcohol followed the cooling curve, all the other samples showed hysteresis, the degree of which varied with cetostearyl concentration. All showed a maximum inflection at between 12–15 °C after which their conductivities decreased until 25 °C. All samples prepared with a cetostearyl alcohol concentration in excess of 1% w/w had measured conductivities at 25 °C after cycling of between 2–3 times those at the start of the experiment. When both the ternary gel containing 10% cetostearyl alcohol and the emulsion (Fig. 2) were cycled a second time they both showed the same shaped curve but, in both cases, their measured conductivities after this second cycle were not significantly different from those after the first cycle. All samples, with the exception of the ternary gel containing 0·5% w/w cetostearyl alcohol, were more viscous and less pourable after temperature cycling. Differential interference microscopy (Patel et al 1985) of the

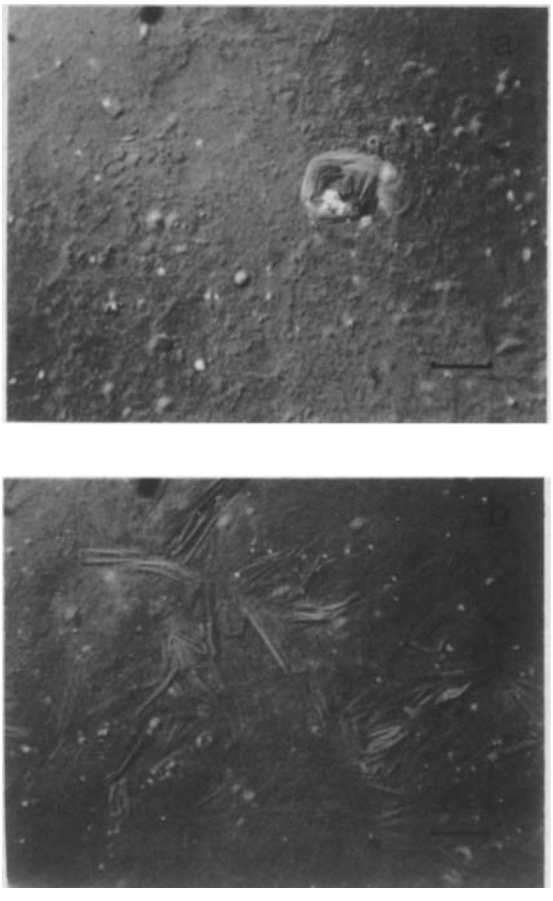
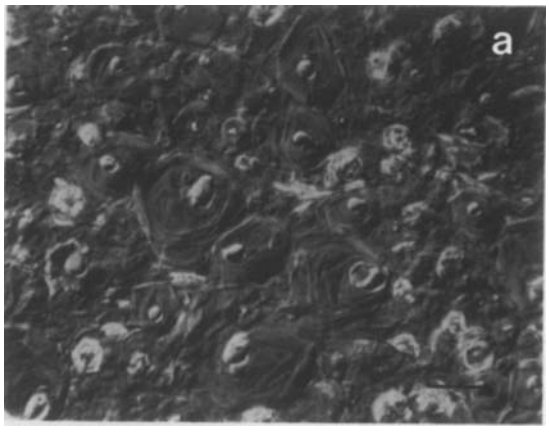
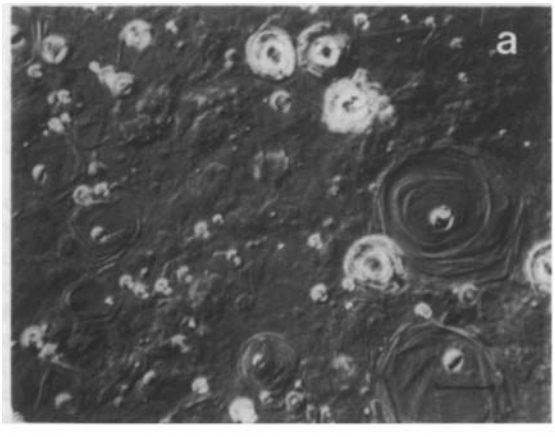


FIG. 3. Differential interference contrast photomicrographs of a ternary gel, T_2, containing 1% cetostearyl alcohol before (a) and after (b) temperature cycling. Note the change in the amount of liquid crystalline network (1 division = 25 μm).

samples before and after cycling showed distinct changes in the amount and orientation of the lyotropic liquid crystalline phase (Figs 3, 4, 5). It can be seen that there is a change from a more ordered structure with the liquid crystalline phase encircling relatively large cetostearyl alcohol particles to one of less order with the liquid crystalline phase extended and more randomly orientated. There does not appear to be any significant change in the size of the cetostearyl alcohol particles after cycling.

The mechanism of this process would appear to be complex. The low conductivity at −5 °C after the samples had attained steady state is almost certainly due to the cetrimide preciptating from solution since an independent experiment with 0·5% w/w cetrimide solution has established a Kraft point of −5 °C for the batch of material used in this work. Thawing of the sample should therefore result in an increase in conductivity





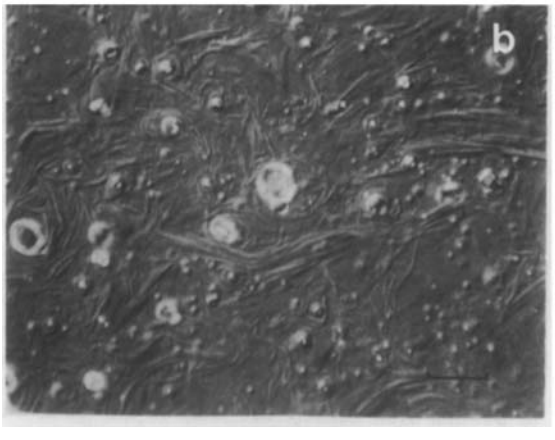


FIG. 4. Differential interference contrast photomicrographs of a ternary gel, T_4, containing 4% w/w cetostearyl alcohol before (a) and after (b) temperature cycling. Note the change in the orientation of the liquid crystalline network (1 division = 25 μm).

FIG. 5. Differential interference contrast photomicrographs of a ternary gel, T_6, containing 10% w/w cetostearyl alcohol before (a), after one cycle (b) and after 2 cycles (c). Note the changes in the orientation of the liquid crystalline network after the second cycle (1 division = 25 μm).

back to the value before freezing. That this only occurs for the ternary gel containing 0·5% w/w cetostearyl alcohol, a sample known not to contain any lyotropic liquid crystalline phase (Patel et al 1985) and that all the other samples exhibited hysteresis proportional to their cetostearyl alcohol concentration, would suggest that the very large increases in conductivity on thawing these samples must either be due to some breakdown of the molecular structure of the liquid crystalline phase and maybe release of some bound cetrimide into solution or a change in the tortuosity of the overall structure of the gel. The evidence from the differential interference microscopy would appear to support the latter mechanism. That the maxima in the hysteresis curves all occurred at the same temperature and that subsequent experiments have shown that this temperature varies with the batch and source of the cetostearyl alcohol used to prepare the gels and emulsions, would suggest that the decrease in conductivity after this point is due to the reaction between the cetrimide in solution and the excess cetostearyl alcohol reforming the liquid crystalline phase. Hence this characteristic temperature is analogous with the T_{pen} reported by previous workers (Lawrence 1959; Barry & Shotton 1968) except that in this case the cetostearyl alcohol is likely to be contaminated having been subjected to the processing involved in the preparation of the gels and emulsions.

Although this mechanism is somewhat speculative, it is supported by the observations on the viscosity of the samples since a more random orientation of the liquid crystalline network would be expected to result in a more viscous system (cf the analogy of a polymer in both poor and good solvents). The data presented, however, do show the wealth of information that can be accrued by a systematic analysis of simple conductivity measurements.

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Ionization constants and partition coefficients of 1-arylpiperazine derivatives

S. Caccia*, M. H. Fong†, R. Urso, *Istituto di Ricerche Farmacologiche 'Mario Negri', via Eritrea, 62-20157 Milan, Italy*

The ionization constant (pK_a) and liposolubilities (log P) of fourteen 1-arylpiperazines were determined by n-octanol/buffer partition. pK_a varied little across the entire series. Log P values ranged from less than 1 to about 2 for the highly lipophilic derivatives of the preset series. The results are discussed in relation to the extent to which these derivatives, known to be centrally active, may enter the brain.

Results have been presented recently (Caccia et al 1982; Fong et al 1982; Caccia et al 1983, 1984a) showing that centrally active drugs bearing an arylpiperazine moiety in the side-chain of their chemical structure may form 1-arylpiperazines during biotransformation in-vivo. In addition, these metabolites, known to be biochemically and pharmacologically active (Fuller et al 1978, 1981; Minard et al 1979; Rokosz-Pelc et al 1980; Maj & Lewandowska 1980; Saari et al 1983; Pettibone & Williams 1984), tend to concentrate in the brain reaching concentrations 4–74 times those in plasma, depending on which arylpiperazine derivative is given (Caccia et al 1984b). In the present study we have investigated the comparative ionization constant (K_a) and lipophilicity, as determined by n-octanol aqueous buffer partition, of fourteen 1-arylpiperazines with a view to making a preliminary assessment of the structure-brain uptake relations in 1-arylpiperazine series.

* Correspondence.
† Present address: Nanjing College of Pharmacy, Nanjing, People's Republic of China.

Materials and methods

The 1-aryl-piperazines used were: 1-(2-pyrimidinyl)-piperazine (PmP) and its *p*-fluoroderivative (*p*FPmP), 1-(2-thiazolyl)-piperazine (TzP), 1-(2-pyridyl)-piperazine (PdP), 1-(2-quinolinyl)-piperazine (QuP), 1-(1,2-benzisothiazol-3-yl)-piperazine (BtP), 1-phenyl-piperazine (PP), and its *o*-methoxy (*o*OCH_3PP), *o*-methyl (*o*CH_3PP), *o*-chloro (*o*ClPP), *m*-chloro-(*m*ClPP), *p*-chloro (*p*ClPP), *m*-trifluoromethyl (*m*CF_3PP) and *p*-fluoro (*p*FPP) substituted derivatives (see Fig. 1 for chemical structures). K_a (20 °C) of 1-aryl-piperazine was determined by ultraviolet titration of 2×10^{-4} M aqueous buffer solutions of the test compound. Buffer solutions (pH 4·5–9·5) were prepared from 0·1 M potassium dihydrogen phosphate and 0·05 M sodium borate; the pH was raised by adding 0·1 M