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COMMUNICATIONS

Solubilization kinetics of n-alkanes by a non-ionic surfactant

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The rates of solubilization of a homologous series of n-alkanes (C_nH_{2n+2}; n = 8–16) into micellar solutions of n-dodecyl hexaoxyethylene glycol ether ($C_{12}E_6$) have been measured at 298 K. A mechanism involving a micellar dissociation–association process previously proposed was found to give an adequate description of the data. Proportionality between the micellar solubilization capacity in the kinetic process and that found at equilibrium could be inferred for such a series of solubilizates which have the same locus of solubilization and packing requirements.

Solubilization of nominally insoluble material is a necessary process for a wide range of phenomena including pharmaceutical delivery systems, animal digestive processes and the sensory processes of smell and taste. Much work done on the fundamental equilibrium aspects of solubilization has been limited to determinations of the equilibrium or saturation solubilization capacities of systems and to the effects of variables on these quantities. Comparatively little attention has been focused upon the kinetics of the process with consequently little being known about its mechanism; whereas it is possible in-vivo that the kinetic information is of more importance than the ultimate thermodynamic equilibrium property. This lack of available kinetic data arose because of the relatively slow nature of the process and the experimental difficulties in following the requisite volume and interfacial parameters. The recently developed drop-on-fibre technique (Carroll 1981) for the study of solubilization rates in surfactant solutions (Carroll 1981; Carroll et al 1982; Ward et al 1985) overcomes some of these problems in a relatively cheap and simple way.

Non-ionic surfactants have use in the extraction of oil-soluble vitamins in-vivo and are widely used in detergents because of their biodegradability and their lack of aggressiveness towards skin. A mechanism has been proposed (Carroll 1981; Carrol et al 1982) for solubilization of oils which are essentially insoluble ($<10^{-6}$ wt%) in water, into aqueous micellar solutions incorporating a step which allows for the total effective time (τ) that a micelle is dissociated within the diffusion layer region of the interface with resultant adsorption of surfactant monomers. A complication in comparing different oils arose (Carroll et al 1982) and it was suggested that the relative ability of the oils to pack inside the micelle had to be accounted for in making the comparison. In the present communication it is suggested that for the homologous series of n-alkanes, C_nH_{2n+2} (n = 8–16), this packing factor, manifested in the proportionality constant between the equilibrium and kinetic solubilization capacities, would be the same, and comparison of different members of the series would be adequately explained in terms of the proposed mechanism.

Methods

Micellar solutions of n-dodecyl hexaoxyethylene glycol ether ($C_{12}E_6$) (Nikko Ltd., Japan) were prepared in triple distilled deionized water.

The oils used were of the highest available purity and were passed through alumina columns before use.

Solubilization rates were determined using the drop-on-fibre technique described previously (O'Rourke 1980; Carroll et al 1982). PTFE fibres of ca 20×10^{-6} m diameter were used and the drop profiles recovered photomicrographically.

Equilibrium solubilization capacities were determined by the visual titration method (Donegan 1985) or by GC methods and were reproducible to better than ± 10%.

Results and discussion

Some measurements of the solubilization rates for the n-alkanes are presented with some values for the equilibrium solubilization capacities in micellar solutions ($C_{12}E_6$). Comparison with rates obtained for n-hexadecane (O'Rourke 1980) showed good agreement.

Linear variations of Δn (n = ratio of drop diameter to fibre diameter) with time (Fig. 1a) were observed for all

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of the alkanes studied and were reproducible to better than ± 5%. Rates derived from the Δn-t plots also showed (Fig. 1b) a linear increase with surfactant concentration above the CMC. This behaviour is similar to that observed for the initial rates of oils solubilizing C_8E_4 (Carroll 1981) and $C_{12}E_6$ (Carroll et al 1982), and may be interpreted in terms of a mechanism where micelles diffuse to the oil/water interface where they either dissociate and adsorb or simply diffuse away. Those which dissociate producing monomers which adsorb at the interface, lead to a concerted desorption of oil and surfactant to form a mixed micelle. Such an approach leads to

$$\frac{dF}{dc} = \frac{\Delta}{2\tau}\,\frac{\bar{V}_o\, b}{a} \qquad (1)$$

where F is the flux of oil into the solution, c is the surfactant concentration; $\bar{V}_o$ is the molar volume of the oil; Δ is the diffusion layer thickness; b is the number of moles of oil solubilized/micelle and a is the number of moles of surfactant/micelle. It can be seen (Fig. 2) that the value of dF/dc increases as the length of the alkane chain decreases.

The solubilization rates observed (Carroll et al 1982) for n-hexadecane and squalane in $C_{12}E_6$ micelles, indicated that the experimental ratio of rates was not that expected from the value of the equilibrium solubilization capacities $(b/a)_{eq}$ and equation (1). The discrepancy was explained in terms of micelle filling and shape factors. Values for the rate were calculated assuming the kinetic values of (b/a) to be proportional to $(b/a)_{eq}$ using equation (1) and normalizing to the $\Delta/2\tau$ value derived from the rate of n-tetradecane solubilization. Good agreement (Fig. 2) was observed between the experimental and calculated values for the homologous series of n-alkanes in the range $10 \leqslant n \leqslant 16$. This agreement does not mean that the desorbing mixed micelles necessarily contain the equilibrium amounts of solubilized oil but that the constant of proportionality relating $(b/a)_{kinetic}$ to $(b/a)_{eq}$ is the same for each member of the series. The steric factors determining the packing of the solubilizate molecules in the micelle interior are likely to be similar for such a homologous series and is implied by the analysis. In the previous case of squalane and hexadecane a different requirement would be expected for squalane which is highly branched. Thus, although it is the effective micellar volume available to the solubilizate, as also inferred by Chiu et al (1984), which determines the observed rate, the details of the actual mixing have to be considered when comparing different oils. Ultimately, this will be expressed in terms of the ideality or non-ideality of the solubilizate mixing in the micelle.

The calculated values were found to be slightly lower than the experimental ones for $n \leqslant 10$. It is probable that for these shorter chains there is a contribution from a diffusion mechanism involving micelles and oil in the aqueous medium (Carroll 1981) arising from the higher water solubility of the shorter alkanes. However, under the conditions of these experiments it was not possible to examine this contribution quantitatively.

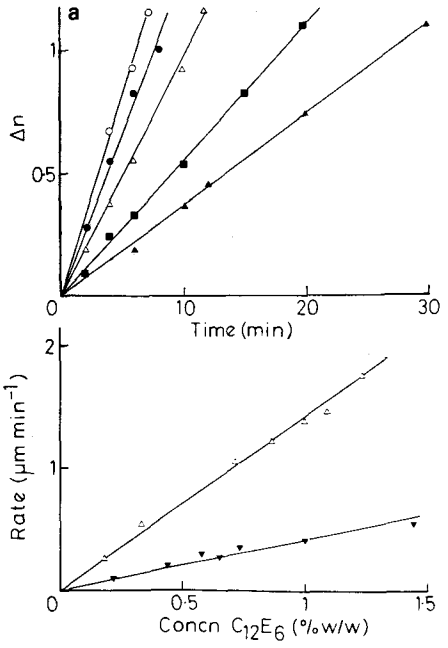

FIG. 1. (a) Solubilization stage of oil droplets at 298 J as a function of time in 0·022 M $C_{12}E_6$ solution: (○) n-octane; (●) n-nonane; (△) n-undecane; (■) n-tridecane; (▲) n-pentadecane. (b) Rate as a function of active concentration for (△) n-nonane and (▼) n-tetradecane.

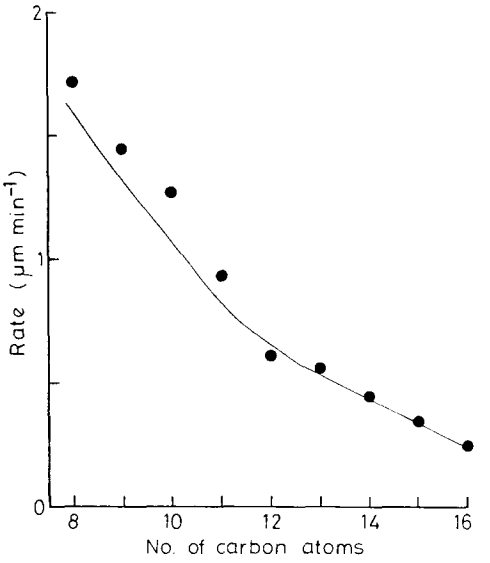

FIG. 2. Rate as a function of the number of carbon atoms per oil molecule in 0·022 M $C_{12}E_6$ solution at 298 K.

An implication of these results is that rates of solubilization from mixtures of these types of oil would be an average of the rates of an individual oil. Preliminary measurements (O'Rourke 1983; Faulkner 1985) indicate this to be the case, in contrast to the observation of selection in equilibrium solubilization (Nagarajan & Ruckenstein 1983) and rates of solubilization (Ward et al 1985) in mixtures of oils with large differences in polarity.

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The effect of polycarbophil on the gastric emptying of pellets

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The influence of the putative bioadhesive, polycarbophil, on the gastric emptying of a pellet formulation, has been investigated in three fasted subjects. The pellets were radiolabelled with technetium-99m. Gastric emptying was measured using the technique of gamma scintigraphy. The pellets emptied from the stomach rapidly and in an exponential manner. Polycarbophil did not retard the gastric emptying of the pellets.

The design of oral controlled release dosage forms continues to attract the attention of formulation scientists. Several technically ingenious systems have been developed, (e.g. osmotic devices) that are capable of well-defined controlled drug release. The performance of these systems in-vivo however, is sometimes limited to the relatively short, and variable gastrointestinal transit times in man (8–10 h) (Ch'ng et al 1985). A device designed to deliver its dose over 24 h, may have emptied from the stomach, traversed the small intestine, and entered the colon in half that time. This could result in a reduced systemic level and a significant fraction of the dose being wasted. Control of the gastrointestinal transit of controlled release systems would be a clear advantage.

The gastric emptying of dosage forms is variable, and influenced by factors such as diet and the type of dosage form administered (Davis et al 1984b). Conversely, small intestine transit appears to be regular and unaffected by these factors (Read et al 1982; Davis et al 1984a). Control of the gastric emptying of dosage forms, therefore, represents the preferred option. A number of strategies have been proposed for this purpose, such as particle size (Meyer et al 1985), particle density (Bechgaard & Ladefoged 1978), and intermittent feeding (Meyer et al 1985). Another approach is the use of so called bioadhesive polymers, which adhere to the mucin/epithelial surface of the gastrointestinal tract (Park & Robinson 1984; Peppas & Buri 1985). Controlled release devices formulated with such polymers, could provide a 'localized platform', in the gastrointestinal tract, for drug release (Longer et al 1985). A variety of polymeric materials has been investigated (Smart et al 1984; Park & Robinson 1985), and anionic, water-insoluble polymers have been proposed because of their low toxicity and greater flexibility of use (Park & Robinson 1984). In particular, polycarbophil, a hydrophilic, granular, acrylate polymer, used as both an antidiarrhoeal, and a bulk-forming laxative (Russell & Bass 1985), has been shown to adhere to the rat stomach and small intestine (Ch'ng et al 1985). Furthermore, a sustained release formulation, containing polycarbophil and albumin beads, provided a longer duration of drug action in rats than formulations without the polymer (Longer et al 1985). It was suggested that polycarbophil rapidly hydrated in-vivo, retaining the beads and adhering to the mucin coating of the rat stomach. No studies have been reported for man.

The gastric emptying of pellets, labelled with a gamma-emitting radionuclide, can be measured in human subjects, using the technique of gamma scintigraphy (Davis 1983). This method has been used in the present study, to investigate the gastric emptying of a pellet formulation containing polycarbophil, in fasted, healthy male subjects. Our results indicate that poly-

* Correspondence.

carbophil does not influence the gastric emptying of the pellets.

Materials and methods

Preparation of formulations. The formulations were prepared in a manner to mirror the systems employed by Longer et al (1985). Pellets (0·5–1·0 mm, density 1·17 g cm^{-3}) of Amberlite IRA410 anionic resin (BDH) were labelled by soaking 6 g in 10 mL [^{99m}Tc]sodium pertechnetate solution (CIS (UK) Limited, London). Size 0 hard gelatin capsules (Capsugel), disintegration time <10 min (BP 1980), were packed with a mix of dried, labelled pellets (310 mg) and 100 mg polycarbophil (0·5–1·0 mm) (Lee Laboratories, Petersburg, USA). Each capsule had an activity of about 3 MBq technetium-99m at the time of administration. The integrity of the binding of the label to the resin, was checked by appropriate in-vitro tests, under relevant conditions of temperature and pH.

In-vivo study. The study was approved by the Ethical Committee of the University of Nottingham and conducted in accordance with the declaration of Helsinki Guidelines for Ethics in Research.

Three, healthy, male volunteers, age range 19–25, height range 1·7–2·0 m, weight range 64–75 kg, participated with informed consent. Each subject abstained from ethanol for 24 h, and had fasted for 10 h before the study. The subjects did not smoke, and were not on medication. On the morning of the study, each subject swallowed one capsule with 100 mL water.

Anterior and posterior images, each of 60 s duration, were taken at regular intervals, using a gamma camera (General Electric Maxicamera, Type II) having a 40 cm field of view and fitted with a low energy (160 keV) parallel hole collimator. The subjects stood in front of the camera for imaging, and remained in upright positions between images. The data were recorded, and stored on computer (Nodecrest). Anatomical reference markers containing technetium-99m, were taped to the skin, anteriorly and posteriorly, over the liver to the right of the stomach. The volunteers were given a standard light lunch (cheese roll, 150 mL orange juice) after 5 h of imaging. After this time they were allowed to eat and drink as normal.

The recorded images were analysed by drawing regions of interest around the position of the stomach.

Table 1. Gastric emptying (t 50% min) of pellets.

Volunteer	Polycarbophil study	Control study
1	53	80
2	23	47
3	80	70
Mean (n = 3)	52	66
s.e.m.	13	8

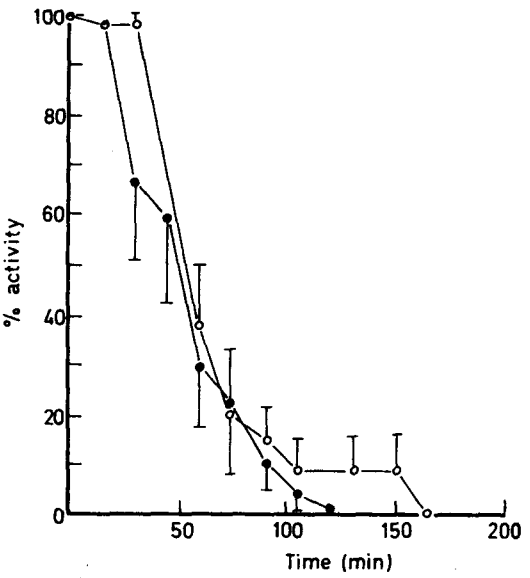

FIG. 1. Gastric emptying of radiolabelled pellets (mean ± s.e.m., n = 3). Key: (●) polycarbophil formulation; (○) control formulation.

The activity in these regions was quantified, and then corrected for background activity and radioactive decay. The error due to the variation in depth of radionucleotide in the stomach, was corrected by calculating the geometric mean of corresponding anterior and posterior views (Tothill et al 1978; Hardy & Perkins 1985).

A control study was conducted one week later, using capsules containing pellets only.

Results and discussion

Gamma scintigraphy was found to be an ideal method for measuring the gastric emptying of the pellet formulations, in fasted subjects. Release of the pellets from the capsule occurred within 15 min of administration and the dispersion of the pellets enabled ready identification of the stomach region for subsequent creation of regions of interest. The images obtained were similar to those presented before (Christensen et al 1985; Hardy & Perkins 1985).

Gastric emptying data have been expressed as the time for 50% (t50) of the pellets to leave the stomach (Table 1). The pooled data have been plotted in Fig. 1, as the mean ± s.e.m. for the three subjects.

The mean t50 gastric emptying time for the polycarbophil formulation, 52 ± 13 min, and for the control formulation, 66 ± 18 min, are in good agreement with previous investigations that have used gamma scintigraphy to measure gastric emptying. Hardy & Perkins (1985) report a t50 gastric emptying of 45 min (n = 4), for pellets given to fasted subjects. The mean t50 gastric

emptying for pellets given to subjects who had taken a light breakfast, was 99 ± 7 min (n = 8) (Christensen et al 1985). Davis et al (1984a) obtained t50 gastric emptying values ranging from 30 to 150 min (n = 6), for pellets taken by subjects who either fasted or had received breakfasts of different calorific values. This influence of food on the gastric emptying of pellets has been well illustrated by Davis et al (1984b). Gastric emptying was slower, 285 ± 45 min, when the subjects (n = 6) received a heavy breakfast, than when given a light breakfast, 119 ± 15 min. Thus, rapid gastric emptying in the present study, can be attributed to the absence of food in the stomachs of the subjects.

Our data show that both formulations empty exponentially (Fig. 1). It has been suggested that particles small enough (≤2 mm) to pass through the 'closed' pylorus, empty more as a liquid than as a solid (Kelly 1981). The rate of emptying of a liquid can be described as an exponential function, and typical t50 gastric emptying times range from 10 to 50 min (Bechgaard 1982). Malagelada et al (1984) report gastric emptying values between 20 and 60 min for radiolabelled water given to fed subjects. Emptying followed approximately an exponential pattern. Similarly, the mean t50 gastric emptying for radiolabelled water, given to subjects who had received a light breakfast, was 18 ± 4 min (n = 5) (Christensen et al 1985). Our results suggest, therefore, that the pellets emptied from the fasted stomach in a pattern similar to that for the gastric emptying of liquids.

The similar rate of emptying for both formulations, indicates that their admixture with polycarbophil does not retard the gastric emptying of pellets in fasted subjects. Longer et al (1985) investigated the gastrointestinal transit of a similar formulation of polycarbophil and albumin beads in rats. Approximately 90% of the beads remained in the stomach 6 h after administration. In the absence of polycarbophil, the beads emptied rapidly. Russell & Bass (1984) have reported that only 8% of a polycarbophil meal emptied from the stomachs of dogs within 90 min. A further investigation of canine gastric emptying of polycarbophil (Russell & Bass 1985) reported that 50% of a 90 g polycarbophil meal emptied within 4 h. However, in this study no attempt was made to attribute the slow emptying to adhesion of the polycarbophil to the gastric mucosa. The amounts of polycarbophil used in those studies, in rat and dog, were greater than that used in the present study and those larger amounts may have elicited motor activity of the fed stomach, which would result in a slower rate of gastric emptying (Russell & Bass 1985).

Our results show that pellets empty rapidly, and with an exponential pattern from the fasted stomach. Admixture of pellets with polycarbophil does not reduce the rate of gastric emptying.

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