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Non-aqueous emulsions: hydrocarbon–formamide systems☆

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Abstract

There are few reports in the literature on formulation of non-aqueous emulsions. This study was designed to evaluate some design criteria for such systems. Formamide is the closest polar solvent that has the ability to replace water in emulsification when employing established non-ionic surfactants as stabilisers. For the majority of studies, linear alkanes (C6–C16) were dispersed in formamide as the continuous phase were stabilised with polysorbate 20. Initial studies involved gentle emulsification and observing mean globule size. The mean globule size varied in a non-linear fashion with alkyl chain length, the minimum being between C10 and C12. Sonication for 30 s led to smaller differences in the mean globule size. The effect of various parameters such as surfactant concentration and solvophilicity of the surfactant was observed. The surface activities of polysorbate 20, 40, 60 and 80 in formamide and critical micellar concentrations were determined. The latter were several orders of magnitude higher in formamide than in water, and the areas per molecule larger. The addition of water to the dodecane formamide systems did not destabilise the emulsion. Release of the model drug dehydroepiandrosterone from dodecane in formamide emulsions was studied in distilled water, the rate of release being dependent on the volume fraction of dodecane.

Keywords: Emulsions; Non-aqueous emulsions; Organoemulsion; Solvophilicity; Formamide; Dehydroepiandrosterone

1. Introduction

In the vast majority of published research in emulsions, one of the liquid phases has been water (Becher, 1965; Florence and Attwood, 1998). Non-aqueous emulsions, however, could replace regular aqueous emulsions wherever the presence of water is undesirable; for example, in cleaning systems that are sensitive to formation of rust, in sol–gel processes with hydrolysable metal alkoxides in organised media, or when incorporating drugs susceptible to hydrolysis. There have been only occasional reports on non-aqueous emulsion systems (Hamill et al., 1965; Hamill and Petersen, 1966a,b; Cameron and Sherrington, 1996).

Non-aqueous emulsions may be of pharmaceutical or cosmetic value if they are composed primarily of edible, non-toxic ingredients and can be

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formulated to exhibit a wide range of physical properties. Some possible uses might be as topical application bases for dermatologicals, particularly for labile drugs, as emollient bases for cosmetic preparations, or as nutrient preparations. We have briefly reported on the formulation of systems based on dodecane and polyethylene glycol (Sakthivel et al., 1999).

Two basic strategies could be considered when searching for stable non-aqueous emulsions. One is to design surfactants having two incompatible blocks, each of which is selectively soluble in either of the immiscible liquids. In this way, diblock copolymers of polystyrene and polyisoprene were able to stabilise DMF/hexane emulsions for almost 24 h (Imhof and Pine, 1997). The other approach is to search for a suitable oil-immiscible polar liquid that can substantially replace water using existing surfactants. Non-ionic surfactants with Hydrophilic lipophilic numbers around 12 were found to stabilise oils dispersed in formamide. The first approach has, of course, the drawback of necessitating the specific design and characterisation of a new surfactant for each combination of liquids (Cameron and Sherrington 1996). The latter approach was adopted in this study.

The emulsifying effects of several ionic and non-ionic surfactants on the non-aqueous, binary system of glycerin and olive oil have been reported (McMahon et al., 1963; Petersen et al., 1964; Hamill et al., 1965; Hamill and Petersen, 1966a,b). Reichmann and Petersen (1973) also studied the effect of temperature on non-aqueous emulsions. Yi and Yang (1999) reported the preparation of microstructures of porous silica in aqueous and non-aqueous emulsion templates. A liquid capable of replacing water in an emulsion should have an appreciable polarity to make it immiscible with oils and to make it a good solvent for the solvophilic part of the surfactant molecules. Hydrogen bonding in the polar liquid is expected to play a role in solvating both ionic and non-ionic surfactants, and in the formation of a hydrogen-bonded network in the liquid itself. The capability of the amphiphile in reducing the surface tension is dependent on the solvent. Hence, as a preliminary step, the surface activity of polysorbates 20, 40, 60 and 80 in formamide was determined.

In the present work, the formulation of non-aqueous emulsions using normal alkanes and formamide is discussed. Dodecane/formamide stabilised with polysorbate 20 was found to be the optimal combination. The release of lipophilic dehydroepiandrosterone (DHEA) from the emulsion was monitored.

2. Materials and methods

2.1. Materials

Formamide (BDH), nonane (Sigma), *n*-decane (BDH), *n*-octane (Fluka), undecane (Fluka), tetradecane (Sigma), hexadecane (Fluka), and polysorbate 20, 40, 60 and 80 (Fluka) were used. ^{3}H-Dehydroepiandrosterone was used as received from Amersham. Water was double-distilled. All other chemicals were obtained from BDH.

2.2. Methods

2.2.1. Determination of critical micellar concentrations

Standard solutions of polysorbate 20, 40, 60 and 80 in formamide and water were prepared in the concentration range 0.001–10 g l^{-1} and the surface tension of each solution was measured using the glass plate method by Dynamic Contact Angle (Cuhn instruments) at 25 ± 0.5°C. An accuracy check on the tensiometer was made by measuring the surface tension of formamide at 25 ± 0.5°C, which was found to be 58.5 ± 0.2 mN m^{-1}.

2.2.2. Preparation of emulsions

The emulsions were prepared by dispersing the *n*-alkanes in formamide at phase volume ratios of 20, 25 and 33% v/v. Polysorbate 20 (1% v/v) was added and the emulsion was stirred for 1 min using the Rota Mixer. Emulsions with similar composition were also prepared by sonication for 30 s using a probe type sonicator.

2.2.3. Stability

The stability of the emulsion was monitored by determining the mean globule size of the emulsion

using a Master Sizer (Malvern, UK) equipped with a stirred sampling unit. Simultaneously, the separation by volume of the disperse phase was quantified.

2.2.4. Release profile

^{3}H-Labelled DHEA, a highly lipophilic drug, was dissolved in dodecane and dispersed in the formamide at volume fractions of 0.20 and 0.33 using polysorbate 20 as emulsifier. One millilitre of the emulsion was placed in dialysis tubing that was subsequently placed in a constantly stirred dialysing medium (distilled water) and maintained at ambient temperature. Samples of 0.1 ml were withdrawn from the dialysing medium periodically and the radioactivity was measured using a liquid scintillation counter. Withdrawn samples were replaced with an equal volume of dialysing medium.

3. Result and discussion

The selection of solvents for formulating non-aqueous emulsion is of importance. The development of a theoretical basis for the selection of the solvent and predicting their respective miscibility and behaviour of a surfactant is required. (Davis and Smith, 1976). The selection of the two phases depends largely on the polarity of the solvents. Stable oil in formamide and oil in polyethylene glycol emulsions could be prepared using commercially available non-ionic surfactants. However, it is relatively difficult to predict the applicability of other polar liquids to serve as the continuous phase. It is still unclear which combination of molecular properties can be used to predict with any certainty a stable system formed with a given surfactant; nevertheless, hydrogen bonding appears to play a pivotal role in determining the stability. However, formamide is closest to water in terms of hydrogen bonding and dielectric constant, and was chosen as the external phase following Imhof and Pine (1997).

The critical micellar concentrations for polysorbate 20, 40, 60 and 80 were determined from surface tension measurements as a function of concentration. Table 1 comprises the values in formamide with those previously reported in water by Wan and Lee (1974). The critical micellar concentrations (CMCs) are higher in formamide, which indicates that formamide is a better solvent for the polysorbates than water. The limiting areas per molecule of the polysorbates in formamide are correspondingly higher than in water.

The formation of the non-aqueous system was studied as a function of the chain length of the *n*-alkanes. Fig. 1 shows that the globule size tends to decrease on increasing the chain length up to C_{10}. A further increase in the chain lengths leads to an increase in the globule size. Emulsions of hexane and the lower alkanes were very unstable. The behaviour could be attributed to the partial solubility of the short chain alkanes in formamide, which in turn leads to destabilisation of the system. The study was further extended to determine of the globule size for the emulsions prepared after sonication (Fig. 2). Although the globule size showed some change with the chain length, significant changes were not observed. The most stable emulsions could be formulated with dodecane as the disperse phase.

Table 1
Critical micellar concentrations (CMCs) and areas per molecule for various polysorbates in formamide and water

	CMC (mol l^{-1})		Area per molecule $(nm)^2$	
	Formamide	Water[a]	Formamide	Water[a]
Polysorbate 20	0.84	0.0053	1.78	0.48
Polysorbate 40	0.21	0.0025	0.96	0.57
Polysorbate 60	0.68	0.0021	1.15	0.53
Polysorbate 80	0.64	0.0011	1.24	0.51

[a] Wan and Lee (1974).

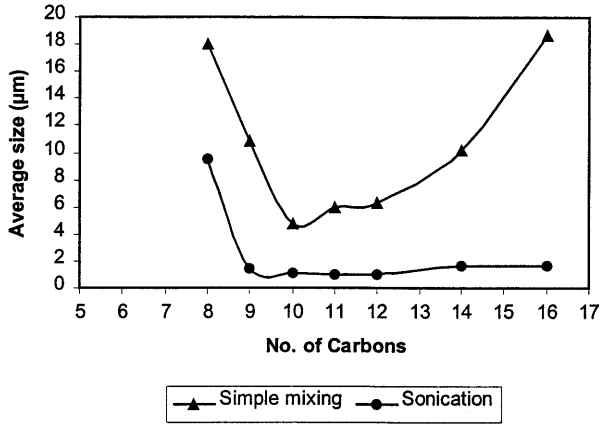

Fig. 1. Effect of carbon chain length on globule size of *n*-alkane–formamide emulsions stabilised with polysorbate 20 prepared by simple mixing and sonication 1 h after preparation (emulsions of hexane are unstable).

The globule size distribution plot of dodecane in formamide with 1% polysorbate 20 is presented in Fig. 4 as a function of time. The globule size of the resultant emulsion did not change over 144 h (Fig. 3). The stability of these emulsions in the presence of 10% water indicated that the system was stable in an aqueous environment. Ten percent of water was considered to be the level that might come in contact with emulsion during dialysis.

The pharmaceutical potential of these systems lies in their ability for entrapping therapeutically active substances and their respective potential for controlled delivery. ^{3}H-DHEA, a highly lipophilic molecule, was added to the internal phase of the emulsion and the radioactivity released in the dialysing medium of distilled water was measured. The release was observed to follow first-order release kinetics (Fig. 4a). Release of ^{3}H-DHEA from the emulsion after 5 h is shown, in Fig. 4b, to be a function of dodecane volume fraction that could be attributed to the relative solubility of the compound in dodecane and formamide.

The field of non-aqueous emulsions is relatively uncharted territory. However, the issues concerning the stability of the emulsions with regard to the pharmaceutically acceptable solvents still require considerable effort. When squalene, a hyperbranched alkane, was used, instability was

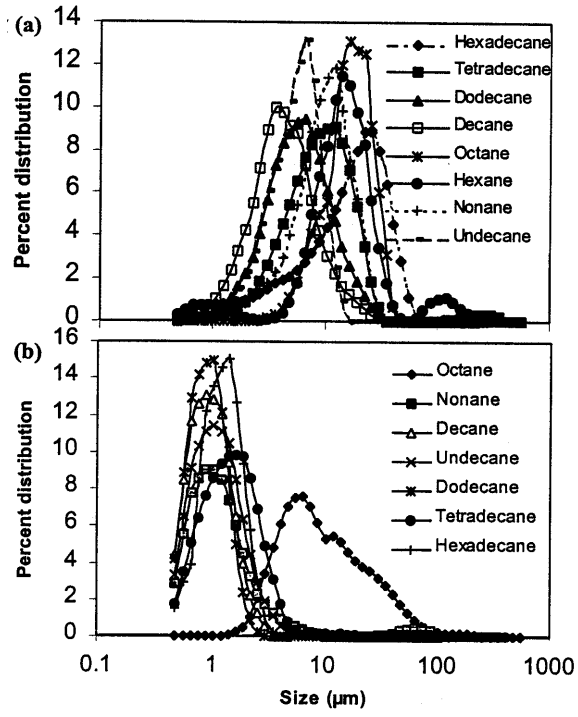

Fig. 2. Effect of carbon chain length on globule size distribution of *n*-alkanes in formamide emulsions stabilised with polysorbate 20 after formation of emulsion by (a) bench shaking and (b) sonication measured after 1 h of preparation.

observed. Replacing the formamide with dimethyl formamide and methyl formamide also leads to instability with the polysorbates, emulsifiers, but

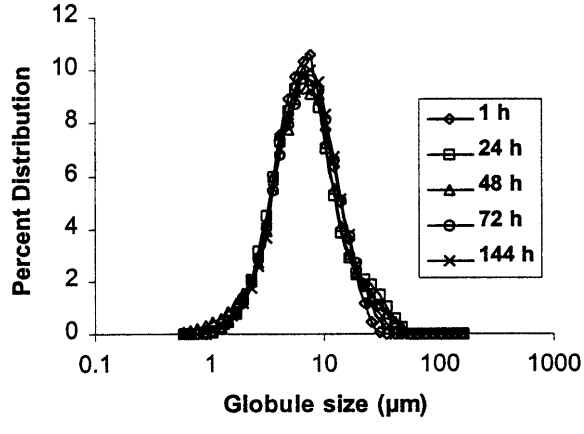

Fig. 3. Effect of ageing on globule size of dodecane–formamide emulsion stabilised with polysorbate 20.

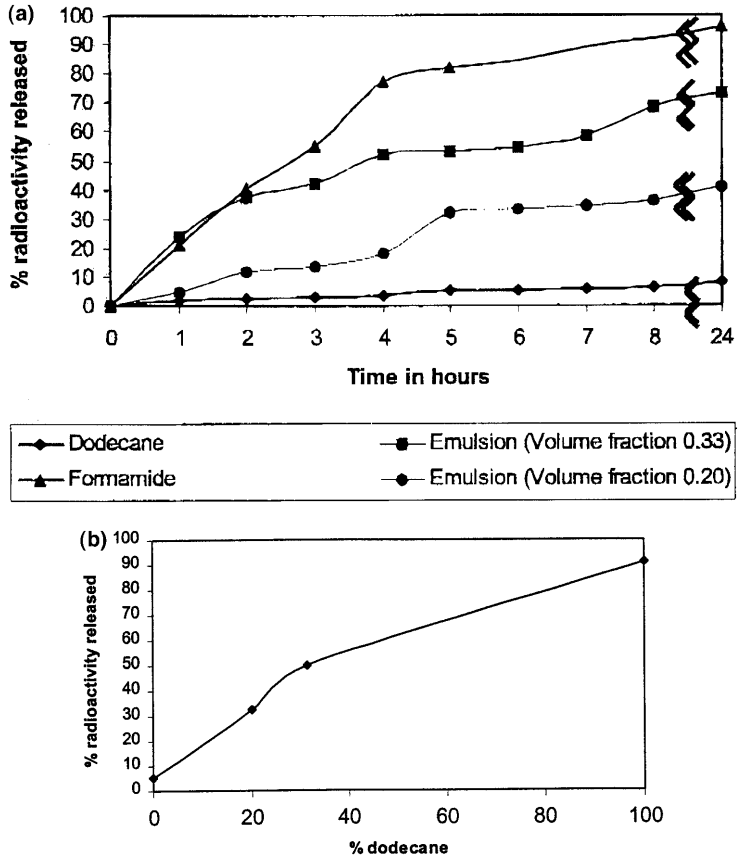

Fig. 4. (a) In vitro release of dehydroepiandrosterone from dodecane/formamide emulsion into water at two volume fractions of 0.2 and 0.33; Release from dodecane and formamide suspension (DHEA does not completely dissolve in formamide) respectively. (b) The influence of dodecane volume fraction on release of ^{3}H-DHEA from dodecane in formamide emulsions after 5 h.

these preliminary findings form the basis for the further work to understand the criteria for choice of suitable surfactant and solvent to formulate stable non-aqueous systems.

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References

Becher, P., 1965. Emulsions:Theory and Practice, 2nd ed. Reinhold, New York.

Cameron, N.R., Sherrington, D.C., 1996. Non-aqueous high internal phase emulsions — preparation and stability. J. Chem. Soc. Faraday Trans. 92, 1543–1547.

Davis, S.S., Smith, A., 1976. In: Smith, A.L. (Ed.), Theory and Practice of Emulsion Technology. Academic Press, London.

Florence, A.T., Attwood, D., 1998. Physicochemical Principles of Pharmacy, 2nd ed. Macmillan, London.

Hamill, R.D., Petersen, V., 1966a. Effect of surfactant concentraion on the interfacial viscosity of a nonaqueous system. J. Pharm. Sci. 55, 1274–1277.

Hamill, R.D., Petersen, V., 1966b. Effects of ageing and surfactant concentration on the rheology and droplet size distribution of a nonaqueous emulsion. J. Pharm. Sci. 55, 1269–1277.

Hamill, R.D., Olson, F.A., Petersen, R.V., 1965. Some interfacial properties of a nonaqueous emulsion. J. Pharm. Sci. 54, 537–540.

Imhof, A., Pine, D.J., 1997. Stability of nonaqueous emulsions. J. Colloid Interface Sci. 192, 368–374.

McMahon, J.D., Hamill, R.D., Petersen, R.V., 1963. Emulsifying effects of several ionic surfactants on a nonaqueous immiscible system. J. Pharm. Sci. 52, 1163–1168.

Petersen, R.V., Hamill, R.D., McMahon, J.D., 1964. Emulsifying effects of some nonionic surfactants on a nonaqueous immiscible system. J. Pharm. Sci. 53, 651–655.

Reichmann, K.W., Petersen, R.V., 1973. Temperature studies with nonaqueous emulsions. J. Pharm. Sci. 62, 1850–1856.

Sakthivel, T., Wan, K.W., Florence, A.T., 1999. Formulation of non-aqueous emulsions. Pharm. Sci. Suppl. 1, 685.

Wan, L.S.C., Lee, P.F.S., 1974. CMC of polysorbates. J. Pharm. Sci. 63, 136–137.

Yi, G.R., Yang, S.M., 1999. Microstructures of porous silica prepared in aqueous and nonaqueous emulsion templates. Chem. Mater. 11, 2322–2326.