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International Journal of Pharmaceutics 298 (2005) 367–371
international journal of pharmaceutics
www.elsevier.com/locate/ijpharm

Note

Novel anhydrous emulsions: Formulation as controlled release vehicles

Orawan Suitthimeathegorn, Vikas Jaitely, Alexander T. Florence *

Centre for Drug Delivery Research, The School of Pharmacy, University of London, 29-39 Brunswick Square, London WC1N 1AX, UK

Received 7 January 2005; received in revised form 10 February 2005; accepted 1 March 2005
Available online 6 June 2005

Abstract

Novel anhydrous emulsions, which may offer some advantages as depot or reservoir vehicles for lipophilic drugs in controlled delivery systems, were formulated using castor oil as the disperse phase and dimethicone or cyclopentasiloxane as the continuous phase. Among the emulsifiers studied only silicone surfactants (cyclomethicone/dimethicone copolyols) which were miscible in silicone oil stabilized the emulsions. Cyclomethicone/PEG/PPG-18/18 Dimethicone and Cyclopentasiloxane/PEG/PPG-18/18 Dimethicone were more effective in lowering the interfacial tension between castor oil and both dimethicone and cyclopentasiloxane. Emulsions formulated using either of these two surfactants were found to be stable against phase separation and exhibited least globule growth over 168 h. The average particle size was found to be 2–6 μm in these systems formed by probe sonication. Slow release patterns of ^{3}H-dehydroepiandrosterone (DHEA) and ^{3}H-dexamethasone solubilized in the disperse castor oil phase into an aqueous dialyzing medium were observed over 48 h.

Keywords: Emulsions; Non-aqueous emulsions; Interfacial tension; Silicone surfactants; Non-ionic surfactants; Depot; Controlled release

Pharmaceutical emulsions are generally oil-in-water (o/w) or water-in-oil (w/o) systems, that is, where one of the liquid phases is water (Becher, 2001). However emulsions can be formulated without an aqueous phase to produce anhydrous, non-aqueous or oil-in-oil emulsions. Such systems, which can replace conventional emulsions where the presence of water is to be avoided, have been used for the preparation of nanoparticles or as templates in the formation of silicate microstructures (Imhof and Pine, 1997a). They might also be useful as vehicles for the slow delivery of injectable drugs.

There is not only a lack of data relating to the formulation of non-aqueous emulsions, but there are relatively few publications on the subject. Hamill and Petersen in the mid-1960s (Hamill et al., 1965; Hamill and Petersen, 1966a,b) explored emulsions of olive oil and glycerin, Reichmann and Petersen (1973) emulsions of glycerin and mineral oil, while more recently Cameron and Sherrington (1996) have reported emul-

* Corresponding author. Tel.: +44 207 753 5819; fax: +44 207 837 5092.
E-mail address: a.t.florence@ulsop.ac.uk (A.T. Florence).

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doi:10.1016/j.ijpharm.2005.03.028

sions of petroleum ether in formamide, DMF and DMSO. We have also formulated anhydrous emulsions, reporting on dodecane in polyethylene glycol systems stabilized by sorbitan trioleate (Sakthivel et al., 1999) and also emulsions of alkanes in formamide emulsified with polysorbate 20 (Sakthivel et al., 2001).

Emulsions with polar continuous phase such as DMSO, DMF and formamide have more similarity with aqueous systems than systems comprising two non-polar oils, which present greater challenges. Since hydrocarbons and formamide are pharmaceutically unsuitable materials, we here report on castor oil-in-silicone oil (polydimethylsiloxane and cyclopentasiloxane) emulsions. One advantage of non-aqueous systems is that the properties of both phases can often be manipulated, for example by varying the molecular weight of oligomeric or polymeric liquids in one of the component phases. Emulsions of castor oil-in-silicone oils of varying viscosity stabilized by the octylphenyl-poly (10) oxyethylene ether (Triton-X-100) have previously been reported by our group. Optimization of the viscosity of the silicone oils was determined (Jaitely et al., 2004). Emulsions comprised of castor oil in silicone oil of different viscosities have also been used as models to study rheological behaviour in an electric field (Ha and Yang, 2000).

The present work was aimed at formulating stable non-aqueous emulsions of castor oil and silicone oil, exploring also the possibility of using such systems as anhydrous vehicles for controlled drug release.

Castor oil (Fluka), cyclopentasiloxane (DC 245) and polydimethylsiloxane polymer (DC 20; Dow Corning grade 200 silicone fluid 20 cSt, UK) were used as the major components. The non-ionic surfactants Tween 60, Tween 85, Span 60, Span 85, Triton X-15, Triton X-100, and Triton X-405 were obtained from Sigma (UK). Other silicone surfactants; PEG/PPG-18/18 Dimethicone (DC 190), PEG-12 Dimethicone (DC 193), Cyclomethicone/PEG/PPG-18/18 Dimethicone (DC 3225C), Lauryl PEG/PPG-18/18 Methicone (DC 5220), Cyclopentasiloxane/PEG/PPG-18/18 Dimethicone (DC 5225C), PEG/PPG-15/15 Dimethicone (DC 5330), and Cyclopentatasiloxane/PEG-12 Dimethicone Crosspolymer (DC 9011) were obtained from Dow Corning (Thailand). ^{3}H-Dehydroepiandrosterone (DHEA) (Dupent/NEN, USA) and ^{3}H-Dexamethasone (Amersham, UK) were used as lipophilic model drugs.

Emulsions were prepared using a Rotamixer or by probe sonication at room temperature. The mean particle size of castor oil (300–500 droplets) in silicone oil emulsion was determined by photomicrography on suitably enlarged prints. The pendant drop method was used to determine the effect of the silicone surfactants on the interfacial tension of castor oil against silicone oil. Digital photography allowed the measurement of the parameters required to calculate the interfacial tension by standard techniques (Adamson, 1990).

^{3}H-Dehydroepiandrosterone (^{3}H-DHEA) and ^{3}H-Dexamethasone were solubilized in the disperse (castor oil) phase. Dimethicone (DC 20) containing the silicone surfactant (DC 3225C), was then added to the drug solution and emulsions with phase volumes (φ) of 0.25 and 0.5 were prepared. The release profile was studied using a dialysis technique and maintained at 37 °C. Samples were withdrawn periodically. The radioactivity was recorded over a 5 min period by a multi-purpose scintillation counter (Beckman LS 6500, USA) with a 5 min measurement time for each sample.

None of the conventional non-ionic surfactants and not all of the silicone surfactants studied could form stable castor oil-in-silicone oil emulsions. Only the three silicone surfactants DC 3225C, DC 5225C, and DC 9011 produced appreciable stability (Fig. 1a). The major approach to achieve stability of non-aqueous emulsions was to find a suitable surfactant whose two structural parts were selectively soluble in either of the immiscible phases, such as the use of diblock copolymers of polystyrene and polyisoprene to stabilize DMF in hexane emulsions (Imhof and Pine, 1997b). Similarly, the silicone surfactants used in this work contained diblock copolymers along with bulky silicone chains. This may have provided an added steric barrier to coalescence and have contributed to the stabilization of the castor oil in silicone oil emulsions.

In addition, only silicone surfactants which were miscible in the continuous phase (either cyclopentasiloxane or polydimethylsiloxane) stabilized the systems, hence the time-honoured Bancroft rule (that an effective stabilizer for a oil-in-water emulsion should be soluble in the continuous and vice versa) (Becher, 2001) applies to these systems. Hence castor oil-in-silicone oil emulsions are emulsified by surfactants soluble in the silicone oil. For example silicone surfactant DC 190, which is soluble in castor oil, stabilizes silicone oil-in-castor oil emulsions (Fig. 1b).

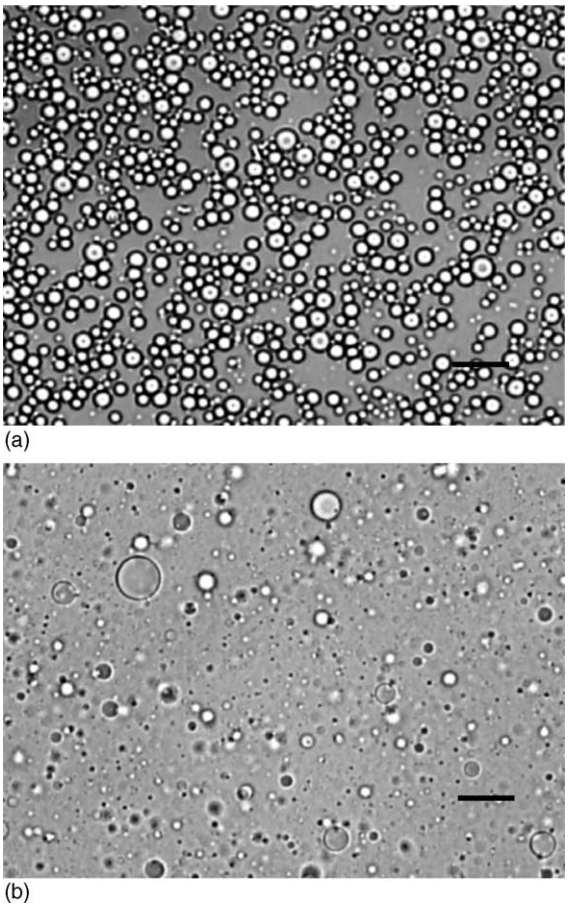

Fig. 1. (a) Photomicrograph of a castor oil in silicone oil emulsion stabilized by the silicone surfactant DC 3225C (Cyclomethicone/PEG/PPG-18/18 Dimethicone). (b) Photomicrograph of a silicone oil in castor oil emulsion stabilized by the silicone surfactant DC 190 (PEG/PPG-18/18 Dimethicone). The scale bar is 10 μm.

The interfacial tension between castor oil and silicone oil (Fig. 2) is decreased more markedly by DC 3225C and DC 5225C than by DC 9011. The interfacial tension–concentration plots indicated that the apparent critical micelle concentration (cmc) values for the silicone surfactants in these systems are approximately at a concentration of 5% (w/v). DC 9011 does not lower the interfacial tension significantly at the castor oil/DC 245 interface (Fig. 2b). The limiting interfacial tensions between castor oil and DC 245 for DC 3225C, DC 5225C, and DC 9011 were 4.65, 4.05, and 21.17 mN/m, respectively.

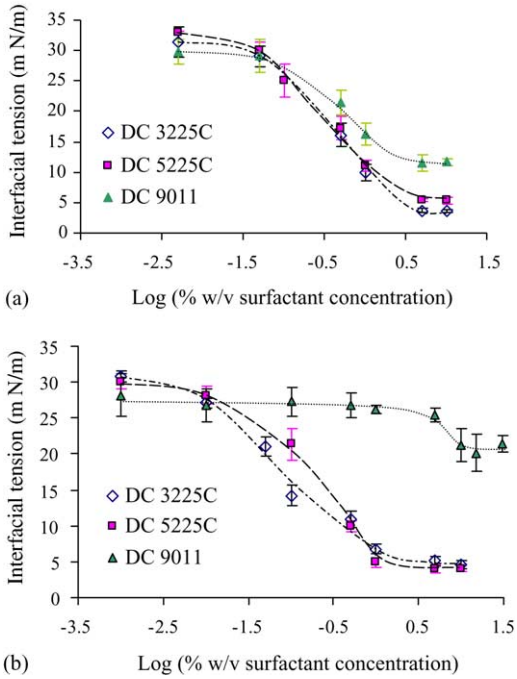

Fig. 2. Plots of interfacial tension of castor oil against two silicone oils dimethicone (DC 20) and cyclopentasiloxane (DC 245) (determined by the pendant drop method) with three silicone surfactants. Solutions of surfactant in the silicone fluids were prepared in the concentration range 0.001–10% w/v. (a) The interfacial tension of castor oil vs. dimethicone (DC 20, viscosity = 20 cSt). (b) The interfacial tension of castor oil vs. cyclopentasiloxane (DC 245, viscosity = 4.2 cSt).

The mean particle size of castor oil in silicone oil emulsions, with a 5% w/v silicone surfactant concentration, was plotted against time up to 168 h (Fig. 3). Of the three surfactants, DC9011 provided the least stable emulsion especially for the castor oil-in-DC 245 system (Fig. 3b), a result correlated with the interfacial tension data.

Using mean particle size as a key parameter indicating stability, castor oil-in-DC 20 silicone oil emulsions were seem to be more stable than castor oil in DC 245 silicone oil emulsions. The higher viscosity of DC 20 compared to that of DC 245 would reduce the collision of globules and slow the draining of the film of continuous phase between the droplets.

Non-aqueous emulsions have potential as vehicles for lipophilic drugs. The release profiles of DHEA and dexamethasone are shown in Fig. 4. At a phase volume ratio of 0.25, the release rate was found to be higher

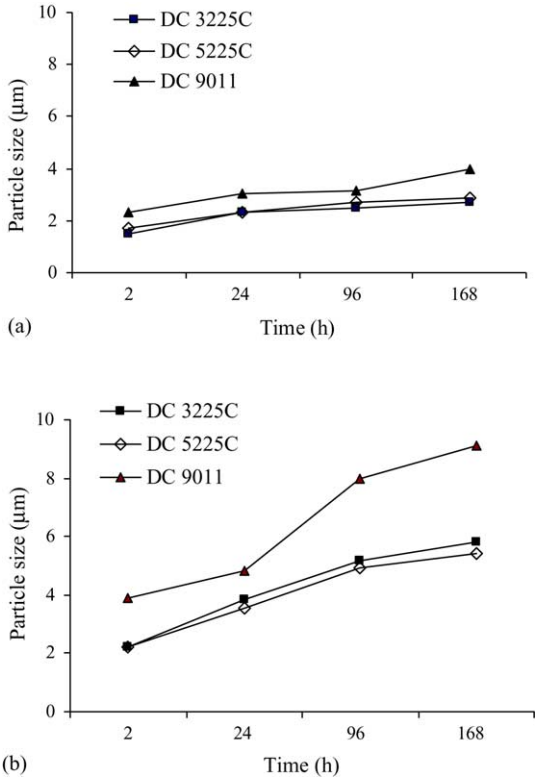

Fig. 3. The change in the mean particle size of castor oil-in-silicone oil emulsions with different silicone surfactants over time. (a) The mean particle size of castor oil-in-dimethicone (DC 20) emulsions and (b) the mean particle size of castor oil-in-cyclopentasiloxane (DC 245) emulsions.

than from emulsions with a phase volume ratio of 0.50, a result which may be explained by the smaller mean particle diameter of emulsions (1.52 μm compared to 4.59 μm) and the resulting larger globule surface area at the lower phase volume.

In summary, we have produced stable anhydrous emulsions of castor oil and silicone oil. The significant factor in the stabilization of the emulsion was the solubility of the surfactants in the continuous phase, lowering of interfacial tension being not in itself sufficient. As there are no guidelines for the selection of surfactants to stabilize two immiscible non-polar oils we are continuing to study a wider range of non-aqueous systems to develop a better understanding of stabilization. Perhaps an analogue of HLB, a lipophile (1)-lipophile (2) balance (L_1L_2B) may be used to predict surfactant choice.

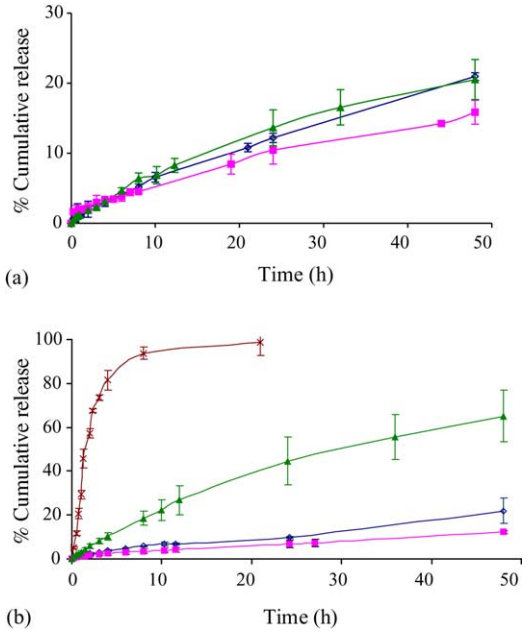

Fig. 4. (a) In vitro release of two lipophilic model drugs from the disperse phase of castor oil-in-silicone oil emulsions into an aqueous dialysing medium (pH 7.4). (a) ^{3}H-DHEA: (◊) phase volume 0.25; (■) phase volume 0.50; (▲) castor oil alone. (b) ^{3}H-Dexamethasone: (◊) phase volume 0.25; (■) phase volume 0.50; (▲) castor oil alone; (×) positive control (to indicate that the dialysis membrane itself was not a barrier for drug to be released).

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