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Review Article

NON AQUEOUS MICROEMULSIONS: NOVEL APPROACH FOR DELIVERY OF POORLY SOLUBLE DRUGS

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ABSTRACT
Non Aqueous microemulsion have attracted a great deal of attention not only because of there importance in industrial application but also there intrinsic interest. They optimize the performance of a wide spectrum of products and processes. Non Aqueous microemulsions are suitable for poorly aqueous soluble drugs and thermodynamically stable multicomponent fluids composed of polar solvent, oil and mixture of a. Liquid administration of drugs is one of the convient and often-advantageous delivery, especially when dealing with children or the elderly for whom pill swallowing can be difficult or even hazardous. Unfortunately many drugs are not soluble in water, while water solution of it may have an unpleasant taste. Some drugs are either unstable in the presence of water or are insoluble in water and therefore cannot be incorporated into aqueous formulations. To overcome these various problems a water free liquid preparation of a number of drugs would be desirable.

KEYWORDS: Non Aqueous microemulsion, poorly aqueous soluble drugs, multicomponent fluids

INTRODUCTION

Over the past few decades there has been growing interest to develop novel drug delivery systems. These system uses to minimize drug degradation and loss, to prevent harmful side-effects and to increase drug bioavailability and the fraction of the drug accumulated in the required zone, various novel drug delivery systems are currently under development. Among drug carriers one can name non aqueous microemulsion.

Non-aqueous systems are well known as solvents for drugs, suspension vehicles, and oleogels. By far, the vast majority of emulsions used pharmaceutically have water as one phase. It is some time since our group actively investigated oil-in-water and water-in-oil-in-water ("multiple") emulsions, but there has been a resurgence of interest in emulsions as delivery vehicles other than for topical delivery, exemplified by the microemulsion formulation of cyclosporin and an intravenous propofol emulsion. Emulsions with no aqueous phase (anhydrous, non-aqueous, oil-in-oil emulsions) have had relatively scant attention, yet should have uses as drug reservoirs as well as templates for the preparation of microspheres and nanoparticles. In the past few years, recognizing that the literature was relatively sparse, we have studied some emulsions of two non-aqueous or "oil" phases. Not only are there no rules for their stabilization, but the normal rules elaborated for the formulation of emulsions containing a non-polar oil phase and an aqueous phase do not hold. There is thus some challenge in producing stable anhydrous emulsions, which might be useful in formulating hydrolytically unstable drugs or to provide reservoir vehicles for transdermal systems.

THE LITERATURE

There are relatively few publications on non-aqueous emulsions. Hamill and Petersen published a number of papers in the early to mid 1960s, Periard in 1970, Reichmann and Petersen in 1973, Cameron and

Sherrington in 1996, and Imhof and Pine in 1997.[1-9] Some authors have used non-aqueous emulsions in the preparation of nanoparticles or as templates in the formation of silicate microstructures, usually without providing details of formulation issues.[10-12] Using a polar liquid, such as formamide as the continuous phase, allows a fairly straightforward approach to formulation, as conventional non-ionic surfactants with a typical non-polar hydrocarbon and polar polyoxyethylene structure will dissolve ready in the continuous phase in a non-aqueous emulsion and behave in the anticipated manner, lowering interfacial tension and providing a stabilising emulsifying layer.[13] The solubility of these surfactants in the continuous phase produces the right conditions for stabilization.

First essay into the field however employed a hydrocarbon as the disperse phase and a more challenging continuous phase, namely polyoxyethylene glycol.[14] One advantage of using oligomeric or polymeric liquids, such as polyoxyethlyene glycols, or silicones as a component phase is that there is the ability to vary the properties of the phases, such as viscosity, by using analogues of different molecular weight. Viscosity might well play a more important role in the stabilization of non-aqueous emulsions than of their aqueous counterparts. In optimization studies we have conducted with castor oil in silicone-oil emulsions, the viscosity of the silicone continuous phase was varied from 1 cSt to 100 cSt. With a non-ionic surfactant as emulsifier, a viscosity of 48 cSt was found to be optimal. It is evident that there should be such an optimum as the energy required to produce small droplets is greater in liquids of the higher viscosity, and a continuous phase having a lower viscosity has a lower ability to inhibit creaming or settling.[15]

In one study of a hydrocarbon in formamide series (pharmaceutically unsuitable but physico-chemically useful), we employed linear alkanes from C_8 to C_{16} as the disperse phase. Simple mixing of the series (stabilized by polysorbate 20) produced a minimum globule size with decane (C_{10}), but preparation by sonication led to the minimum size being achieved with the C_{10} to C_{12} alkanes; only octane produced coarse emulsions.

SILICONE (DIMETHICONE & CYCLOPENTASILOXANE) EMULSIONS

Most recent work has focused first on castor oil in dimethicone or cyclopentasiloxane and secondly on these silicones in castor oil. It is clear that in non-aqueous systems, some modes of stabilization do not apply, enthalpic stabilization due to the loss of solvation as occurs with polyoxyethylene chains at aqueous interfaces will not occur, particularly when the solvent phase is itself composed of oligomeric molecules. Steric stabilization may also be less pronounced when the molecular weight of the continuous phase is high. A physical protective effect can be imagined with the complex structures of a siloxane copolymer surfactant to achieve a physical barrier, the surfactant must lower interfacial tension, but the interfacial film must also be sufficiently viscoelastic to protect the surface. While both alkyl and aryl poly(oxyethlyene) ethers and silicone-based surfactants lower interfacial tension at the castor oil-silicone interface, a dominant factor in ensuring stabilization is the solubility of the surfactant in the continuous phase, which of course is a manifestation of the Bancroft rule for conventional emulsions. Solubility is, of course, not in itself sufficient, but a lipophile 1-lipophile 2 balance (L_1L_{2B}) scale is required for non-aqueous systems not least because of the potential diversity of the phases. At least in aqueous emulsions, water is a constant! A micellar reservoir in the continuous phase provides surfactant for elasticity. Of the conventional surfactants, linear alkyl non-ionic surfactants had little effect on stabilization, while alkyl-aryl surfactants, such as those of the Tergitol NP series or Triton X series, did achieve stabilization of castor oil and silicone-oil systems. Not all silicone surfactants can achieve stabilization. We are still unravelling these complex effects in an attempt to achieve some rules for the formulation of these interesting systems.

RESERVOIR EFFECTS

Fig 3: shows data on the release of a model drug dissolved initially in the disperse phase DHEA of castor oil/dimethicone or castor oil/cyclopentasiloxane emulsions into an aqueous reservoir. This shows the ability to modulate release. Reiss et al discussed recently non-aqueous emulsions of polyoxyethlyene glycol mixed with a biocide in a thermoplastic elastomer in methylcyclohexane, in which solvent evaporation leads to an elastomeric film bearing biocides.[16]

MULTIPLE SYSTEMS

Having formed oil-in-oil systems, it follows that multiple systems can also be formulated. Either $o_1/o_2/o_1$ systems or $o_1/o_2/w$ formulations are possible. Examples of both from our laboratory are shown in Figure. These expand the portfolio of emulsions containing inmmissible oils. A recent paper has reported a novel multiple emulsion system: emulsions of an ionic liquid stabilized by nanoparticles.[17]

MAGNETIC SYSTEMS

Incorporation of magnetite nanoparticles into the disperse phase of these oil-in-oil emulsions has allowed control of the flow of droplets of the phase in capillaries, important in microfluidic systems and also in the design of pulsatile drug release systems.[18] Magneto- and electrorheological systems are of increasing interest in controlling the properties of delivery devices.

CONCLUSIONS

A challenge remains to take the formulation beyond the semi-empirical by developing L_1L_{2B} systems, probably based on the solubility parameters of the oil phases and the surfactant stabilizers. Well-stabilized systems will, we predict, find uses in controlled .subcutaneous depots of these non-aqueous systems.

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Table 1 : Non Aqueous Emulsion Compositions

SN	Disperse Phase	Continuous Phase	Surfactant
1	Olive oil	Glycerin	Anionic, Cationic
2	Dodecane	Formamide	ionic
3	Dodecane	DMSO	Non-ionic
4	Liquid crystals	Silicone oil	Non-ionic
5	Silicone oils	liquid crystals	Non-ionic
6	Dodecane	Formamide	Anionic, Cationic
7	Castor oil	Silicone oil	Non-ionic
8	Dodecane	Poly oxyethy-lene glycol	Non-ionic
9	Castor oil	Dimethicone	Non-ionic
10	Dimethicone	Castor oil	Non-ionic
11	Non -aqueous polar solvent Propylene glycol Formamide	Silicone oil	Anionic and Non-ionic
12	Dodecane	Poly oxyethy-lene glycol	Non-ionic

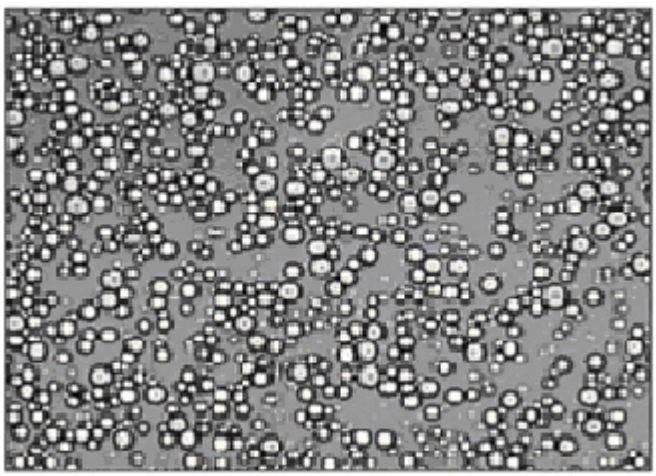

Figure 1: A Photomicrograph of castor oil-in-silicone oil emulsion

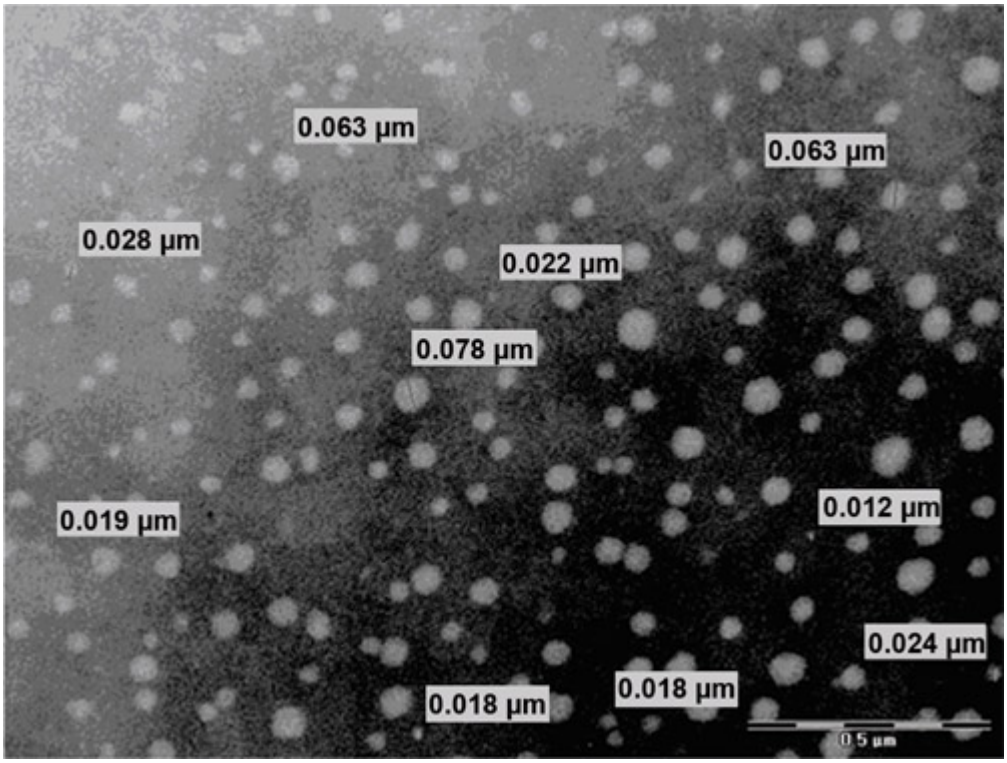

Figure 2: Transmission electron microscopy of castor oil-in-silicone oil emulsion

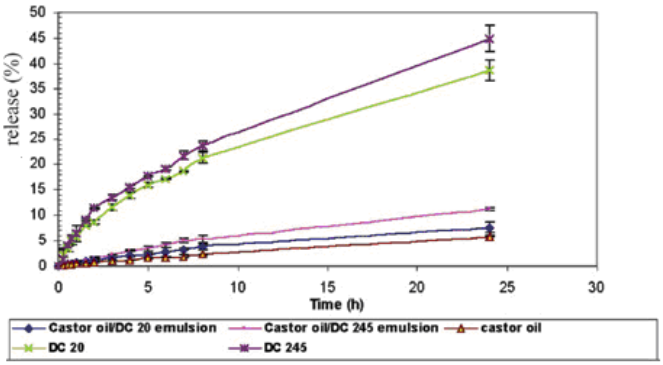

Figure 3: Data on the release of a model drug dissolved

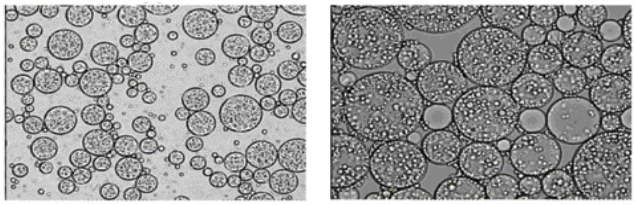

Figure 4: $o_1/o_2/o_1$ systems or $o_1/o_2/w$ formulations

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