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In-situ phase transition from microemulsion to liquid crystal with the potential of prolonged parenteral drug delivery

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ABSTRACT

This study is the first to investigate and demonstrate the potential of microemulsions (MEs) for sustained release parenteral drug delivery, due to phase transition behavior in aqueous environments. Phase diagrams were constructed with Miglyol 812N oil and a blend of (co)surfactants Solutol HS 15 and Span 80 with ethanol. Liquid crystal (LC) and coarse emulsion (CE) regions were found adjacent to the ME region in the water-rich corner of the phase diagram. Two formulations were selected, a LC-forming ME and a CE-forming ME and each were investigated with respect to their rheology, particle size, drug release profiles and particularly, the phase transition behavior. The spreadability in an aqueous environment was determined and release profiles from MEs were generated with gamma-scintigraphy. The CE-forming ME dispersed readily in an aqueous environment, whereas the LC-forming ME remained in a contracted region possibly due to the transition of ME to LC at the water/ME interface. Gamma-scintigraphy showed that the LC-forming ME had minimal spreadability and a slow release of ^{99m}Tc in the first-order manner, suggesting phase conversion at the interface. In conclusion, owing to the potential of phase transition, LC-forming MEs could be used as extravascular injectable drug delivery vehicles for prolonged drug release.

1. Introduction

It has been estimated that 40% of newly discovered drugs have solubility problems, either in oil or in water (Kini et al., 2011), which presents a challenge to formulation scientists particularly with parenteral injectable formulation development. Injectable formulations should usually be in a liquid form and optimized not only for solubility and stability, but also for injectability and tissue tolerability. Although complete solubilization of the drug is not a prerequisite for extravascular injections such as subcutaneous and intramuscular administrations, and suspensions and microparticles are commercially available, particle size control and physical stability of these particulate systems can be significant hurdles in formulation development particularly during large scale manufacture. A number of solubilization approaches have been investigated for parenteral formulations, including the use of organic co-solvents, pH adjustment or salt formation, addition of surfactant or formation of inclusion complexes with cyclodextrins (Strickley, 2004). The parenteral formulations resulting from these approaches are conventionally used to establish rapid onset of drug action. A frequent problem encountered with these conventional formulations is post-administration drug precipitation at the injection site, due to the rapid release of a poorly water soluble drug into the body's aqueous environment (Wu et al., 2010a,b). To this effect, sustained release formulations, modulating the drug concentration at the injection side, may provide a solution (Wu et al., 2010a). Recently, various in situ forming injectable gels emerged as controlled and sustained drug delivery systems due to the ease, and reduced frequency, of administration (Liu and Venkatraman, 2012; Nirmal et al., 2010). However these aqueous based systems have limited solubilizing capacity.

Microemulsions (MEs) are transparent, thermodynamically stable, colloidal systems that form spontaneously when suitable combinations of water, oil and surfactant with a co-surfactant are mixed (Gabriele et al., 2006; Talegaonkar et al., 2008). They are easy to prepare and have low viscosity with the capacity of solublizing both lipophilic and hydrophilic drugs (Alany et al., 2001). Hence MEs have evolved as novel parenteral delivery vehicles for both oil- and water-soluble drugs (Date and Nagarsenker, 2008; Gupta and Moulik, 2008). MEs as parenteral delivery systems for poorly soluble drugs, including a few anticancer drugs, have shown distinct advantages over solvent based formulations including; bioavailability improvement (Date and Nagarsenker, 2008), longer resident time in the blood circulation (Zhang et al., 2006) and a reduction in drug irritation (Lee et al., 2002).

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Liquid crystals (LCs) also consists of water, oil and surfactant(s), and have been explored as drug delivery systems due to their unique characteristics (Mueller-Goymann and Hamann, 1993). LCs are semisolids with crystalline structures combining properties of both solid and liquid states (Hans, 1980). The crystalline structures of LCs render the systems highly viscous; as a result the diffusion coefficient of a drug within a LC phase is about half the magnitude compared to that in solution (Mueller-Goymann and Frank, 1986). This feature has been exploited for sustained drug release following topical administration (Mueller-Goymann and Frank, 1986; Mueller-Goymann and Hamann, 1993). However, a limitation of the high viscosity is that LC systems cannot usually be injected.

Therefore, a system which transitions in an aqueous environment, such as tissue fluids, from a low viscosity ME to a high viscosity LC is envisioned to be highly promising for parenteral injections with the possibility of achieving prolonged drug release. This in situ phase transition concept was reported by Mueller, who used reverse micellar solutions as the medium vehicle which transitioned to a LC system after contact with water and subsequently demonstrated a sustained release rate (Mueller-Goymann and Hamann, 1993).

So far, little research has been carried out to investigate the phase transition behavior of ME formulations in contact with an aqueous environment, specifically the effects of formulation spreadability and drug release. The aim of the present study was to develop two different ME formulations, one with the potential to form liquid crystals and another with the potential to form a coarse emulsion upon contact with water. These formulations were characterized and compared with respect to spreadability and in vitro drug release following phase transition in an aqueous environment to simulate in vivo behavior.

2. Material and methods

2.1. Materials

Solutol HS 15 (Macrogol 15 Hydroxystearate, hydrophilic–lipophilic balance, HLB = 15) was provided by BASF, Fine Chemicals Division, Germany. Span 80 (Sorbitan monooleate, HLB = 4.3), Soybean oil, Nile Red, methylene blue and dialysis tubing cellulose membrane (M.W. 12,000 cut-off) were all purchased from Sigma–Aldrich NZ Ltd., New Zealand. Miglyol 812N, a mixture of medium chain triglycerides, was purchased from Sasol GmbH Oleochemicals, Witten, Germany. Milli-Q water was prepared using the Milli-Q water purification system (Millipore Corp., MA, USA). Absolute ethanol was purchased from ECP-Analytical Reagent ECP Ltd., NZ. Propylene glycol was purchased from Unilab, Ajax Laboratory Chemicals, Australia. Acetonitrile was supplied from Merck KGaA, Germany. Progesterone was purchased from Pfizer Inc. (NY, USA). The raw isotope Molybdenum (Mo-99) was supplied from ANSTO, Australia, to produce the radioactive agent sodium pertechnetate (^{99m}Tc), using a Gentech Technetium Generator (ANSTO, Sydney, Australia). All chemicals and reagents used were of analytical grade, without further purification.

2.2. Formulation development

2.2.1. Construction of pseudo-ternary phase diagrams

The pseudo-ternary systems were prepared using the titration method based on Miglyol 812N (oil), Milli-Q water and a mixture of Solutol HS 15 and Span 80 (surfactants) and ethanol (cosurfactant). The weight ratio between Solutol HS 15, Span 80 and ethanol was 3:1:0.5. The mixtures of oil:surfactant ranging at a constant ratio from 10:90 to 90:10 (w/w), were titrated with Milli-Q water under constant magnetic stirring at ambient temperature (20 °C) at 1% increments of water. Formulations were prepared in parallel at ambient temperature (approximately 20 °C), and were stored at either 20 °C or 37 °C for 24 h before observation was made for the construction of pseudo-ternary phase diagrams at each temperature.

2.2.2. Visual observation and polarized light microscopy

Visual observation and polarized light microscopy (DM RXP, Leica DMR, Germany) were used to identify LCs, MEs and CEs. LCs were identified as semisold systems exhibiting birefringence under cross-polarized light microscopy due to their double refraction property. Clear-transparent samples with an isotropic appearance under cross-polarized light microscopy were regarded as MEs. Samples with phase separation under phase-contrast microscopy and no birefringence under polarized light microscope were classified as coarse emulsions (CE).

2.2.3. ME formulation selection

From the pseudo-ternary systems two different ME formulations were selected; one with the potential to form liquid crystals (LC-forming ME), and another with the potential to form a coarse emulsion (CE-forming ME) upon contact with water. Consideration was given to the viscosity for injectability and the influence of temperature.

2.3. Characterization of MEs

Besides the selected ME formulations, samples were selected from dilution lines A and B (Fig. 1), for various characterization studies. These formulations contained 45:55 and 20:80 (w/w) oil: surfactant/cosurfactant combinations, respectively, possibly representing the changes to the selected MEs as a result of the diffusion of water into the formulations.

2.3.1. Rheological property

Viscosity was measured with a Brookfield DV-III cone and plate rheometer (Brookfield Engineering Laboratories Inc., USA) fitted with a CP-40 spindle. The sample cup was connected to the circulating water bath maintained at 20 °C or 37 °C. A sample volume of 500 μl was used. The measurements were made from 0–240 rpm in triplicate. Data analysis was performed by Rheocalc V3.1 operating software (Brookfield Engineering Laboratories Inc., USA). Viscosity values were recorded at 20 rpm.

2.3.2. Dynamic light scattering (DLS) measurements

Dynamic light scattering (DLS) was used to determine the droplet size of selected formulations distributed along the dilution line A and B. The measurements were made with a Malvern Zetasizer Nano ZS instrument (Malvern Instruments, U.K.). The instrument contained a 4 mW He–Ne laser operating at 633 nm and non-invasive backscattering optics. The measurements were made at a detection angle of 173° and the measurement position was automatically selected by the software. The viscosity of the formulations investigated was used as the viscosity of the dispersant. Each measurement was made in triplicate at 20 °C and 37 °C and subsequently the average droplet size (Z-Average) and Polydispersity Index (PDI) was calculated as a measure of homogeneity of the sample in size.

2.3.3. Transmission electron microscopy (TEM) analysis

Morphology and microstructure of the selected formulations were studied using freeze fracture Transmission electron microscopy (FF-TEM) at an acceleration voltage of 120 kV and typically viewed at a range of magnification of 25,000–88,000×. The