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The role of lecithin degradation on the pH dependent stability of halofantrine encapsulated fat nano-emulsions

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ABSTRACT

We report on the successful incorporation of the antimalarial drug, halofantrine, into laboratory based soybean oil emulsions which were designed to mimic the commercially available parenteral fat emulsion, Intralipid®. A high pH (minimum of pH 9, preferable pH of 11) was required for the drug laden emulsion to remain stable on storage and also to resist breaking under various stresses. Ageing of lecithin samples on storage was noted to result in degradation and a decrease in pH. We argue that this is the main reason for a similar decrease in pH for lecithin based emulsions and subsequent instability in drug laden emulsions. As expected, incorporation of the drug (halofantrine) resulted in lower stability. The (intensity weighted) particle size increased from 281 nm for the drug free emulsion to 550 nm following a loading of 1 g L^{-1} of halofantrine, indicative of a lowering in stability and this was reflected in a shorter shelf life. Interestingly, incorporation of even higher concentrations of drug then resulted in better stability albeit never as stable as the drug free emulsion. We also report on unusual and complex surface tension behaviour for fresh lecithin where multiple critical concentration points were observed.

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1. Introduction

Many efficacious drugs are hydrophobic with poor aqueous solubility and this limits their bioavailability both during and after oral administration (Muller et al., 2004; Fahr and Liu, 2007). An obvious way to overcome this problem is with the use of emulsions which allow the solubility of hydrophobic material into a water based medium (Dardel et al., 1976; Burnham et al., 1982; Muller et al., 2004; Marin-Quintero et al., 2013; Shah et al., 2015). Such drug delivery systems can increase the efficacy of those drugs by ensuring their bioavailability and minimising drug loss through insolubility (Humberstone et al., 1997; Khoo et al., 1998; Fahr et al., 2007; Holm et al., 2011; Caliph et al., 2012). In many cases, where the window between drug effectiveness and drug toxicity is small, this is of crucial value (Krishna et al., 1993; Borrmann et al., 2004; Mosqueira et al., 2006; Haas et al., 2009; Caliph et al., 2013). The modern trend, however, is for more and more complexity in the development of nano-based systems (Mosqueira et al., 2006; Thomas et al., 2012; Shah et al., 2015, 2016a; Allijn et al., 2016; Doktorovova et al., 2016). Many techniques involve excipients which have limited bio-compatibility and/or require hazardous solvents during their preparation (Humberstone and Charman, 1997; Dorota, 2015; Hayes et al., 2016). Other techniques result in emulsions which have only limited shelf-life and/or poor uptake of the drug (Muller, 2004; Fahr and Liu, 2007 Fahr and Liu, 2007). There is, then, a continued need to develop drug delivery systems which are based solely on biocompatible ingredients, which are simple, inexpensive and safe to carry out, and which result in a high yield of drug with good shelf life. There is also a need to understand more fully the mechanism and origin of instability in drug laden colloidal based delivery systems.

The specific drug of interest in this paper is halofantrine (log P = 8.3–9.2), known for its efficacy as an anti-malarial (Khoo et al., 2000; McIntosh et al., 2004; Mosqueira et al., 2006; Leite et al., 2007; Holm et al., 2011, 2012; Caliph et al., 2012; Thomas et al., 2012). We would expect, however, that any findings would be equally applicable to other anti-malarial, hydrophobic drugs including those slightly less hydrophobic than halofantrine

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including atovaquone (log P = 4.7–5.8), quinine (log P = 3.5–4.0), mefloquine (log P = 3.1–4.0), artemisinin (log P = 2.4–3.0), pyrimethamine (log P = 2.6 −2.7), (log P = 1.9–2.5), clindamycin (log P = 1.7–2.2), and the sulphonamides (log P = −1.0–2.0) (Gay et al., 1990; Krishna et al., 1993; Lefevre et al., 2002; Lell and Kremsner, 2002; Borrman et al., 2004; Esamai et al., 2005; Goodman et al., 2007; Leite et al., 2007; Valeyre et al., 2008; Haas et al., 2009; Pull et al., 2013; Oga and Singh (2016).

1.1. Halofantrine (Hf)

The chemical structure of Hf is given in Fig. 1. The base has a pK_a of approximately 9 (Taillardat-Bertschinger et al., 2003), however stability constants of many species are well known to be influenced by surface charge (Tsu et al., 1986; Taillardat-Bertschinger et al., 2003) so this is likely to be modified in the presence of soybean oil (SBO), particularly if the drug partitions to, or close to, the surface of oil droplets. Hf exists as a racemic mixture of both (+) and (−) enantiomers. Its major metabolite, N-desbutylhalofantrine also has two enantiomers.

Like most anti-malarial drugs, reduced sensitivity with widespread use is of concern and has been known since the early 1990s (Gay et al., 1990; Woodrow and Krishna, 2006). The absolute bioavailability of Hf when administered orally is very low (Ajayi et al., 1999). Whilst Hf is poorly soluble in water, it is oil soluble and bioavailable when dissolved in food lipids such as SBO (Holm et al., 2011). Attempts to formulate directly into commercial SBO parenteral emulsions (e.g. Intralipid®) have met with mixed success. Early attempts, for example, proved time consuming and resulted in emulsions of stability only up to one day (Humberstone, 1995) or one week (Khoo et al., 1998), although more successful prototypes were subsequently identified (Charman and Porter, 1999). Halofantrine is thus an ideal candidate to attempt formulation into a biocompatible, lipid-based emulsion.

1.2. Intralipid®

Intralipid® is an SBO-based emulsion originally designed, and still used, for intravenous feeding of patients who are unable to obtain sufficient nourishment orally. Given its simplicity and biocompatibility, it is an ideal choice to base drug delivery systems on.

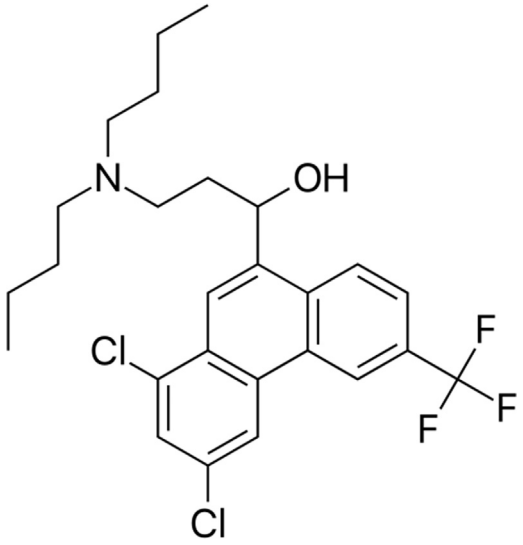

Fig. 1. Chemical structure of halofantrine (Base Form).

Intralipid®, in its simplest form, contains an aqueous dispersion of SBO (10%, 20% or 30%), lecithin (purified egg phospholipids) as the emulsifier, and glycerol to help solubilise the lecithin and to provide the formula with isotonicity (Washington, 1992; Bach et al., 1996; Marin-Quintero et al., 2013).

1.3. Stability of Intralipid®

Commercial Intralipid® is typically stable for one to two years (Washington, 1990) with instability generally caused by the irreversible degradation of the oil and/or the emulsifier. The exact effect is complicated, with small amounts of degradation products sometimes enhancing emulsion stability (Herman and Groves, 1993), but larger amounts causing instability (Grit and Crommelin, 1993).

The release of free fatty acids decreases the pH of the emulsion (Langner et al., 1995; Washington and Davis, 1987; Herman and Groves, 1993; Han et al., 2001; Dorota, 2015). However, the rate of free fatty acid release has been reported to be slower than the rate at which the pH drops (Herman and Groves, 1993) so the exact mechanism for pH changes is not fully known. Nonetheless, even slight changes in pH can induce instability in SBO emulsions, particularly if the emulsion has a low zeta potential and is thus close to its critical flocculation point (Washington, 1990).

1.4. Lecithin

Doktorovova et al. (2016), amongst others, have expressed concerns that whilst the oil in pharmaceutical emulsions may be safe for human use, the surfactant used to stabilise the emulsion may not be. Lecithin is widely available both naturally in food and as a food supplement. It is biocompatible and inexpensive (Grit and Crommelin, 1993; Muller et al., 2004; Mosqueira et al., 2006; Marin-Qintro et al., 2013; Beri et al., 2014), making it an excellent choice for use as the surfactant in emulsions for human use.

The degradation of lecithin and its effect on emulsion stability can be complex. Released free fatty acids can interact with surfactant bilayers (Washington and Davis, 1987) and promote stability. More likely, however, they decrease the pH of the solution and thus the stability of many emulsions including Intralipid® (Grit and Crommelin, 1993; Han et al., 2001; Han and Washington, 2005). On storage, lecithin degradation is probably also a trigger for degradation of emulsion lipids resulting in enhanced degradation of the entire emulsion (Liu et al., 2013). The role of lecithin degradation, and particularly its pH dependence, is therefore important to study in the context of the overall emulsion's stability.

1.5. Encapsulation of drugs using Intralipid® and Intralipid®-like formulations

Arguably the best-known drug to be encapsulated into Intralipid® has been diazepam (Dardel et al., 1976) and its commercial success is encouraging for the choice of Intralipid® as the delivery system. Once injected, encapsulated drugs from simple emulsions are released quickly and simply due to diffusion processes (Salmela and Washington, 2014). Unless sustained or time release drug delivery is required such rapid, internal release of drugs is desirable. The concern, with simple emulsions, is that drugs may also be released quickly on storage, which would be a loss and needs to be minimised. With appropriate formulation, however, emulsion based drug delivery systems can remain stable and remain encapsulate for long periods of time (Shah et al., 2014a).

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