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Kinetically stable propofol emulsions with reduced free drug concentration for intravenous delivery

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ABSTRACT

Purpose: Intravenous injections of propofol emulsions are accompanied by pain likely due to the interaction of the dissolved drug with endothelial cells of the vasculature. It is commonly hypothesized that reducing the aqueous phase concentration of propofol could reduce pain.
Methods: To minimize the propofol concentration in the aqueous phase, we developed stable oil-in-water emulsions with excipient oil mixtures that have an increased partition coefficient for propofol. We then explored the emulsion stability by measuring size distributions after extended durations of shelf storage and also after freeze–thaw cycling. The effects of oil type, surfactant and salt concentration on emulsion stability were also explored.
Results: Small chain oils like ethyl butyrate exhibit high drug partitioning but poor stability, while larger molecules such as soybean oil exhibit lower partitioning but excellent emulsion stability. Emulsions with mixtures of soybean oil and ethyl butyrate are stable for longer than a year, resistant to freeze–thaw cycling, and reduce aqueous drug concentrations of propofol twofold compared to pure soybean oil emulsions.
Conclusions: Oil-in-water emulsions of propofol formulated with mixtures of ethyl butyrate and soybean oil are kinetically stable and significantly reduce the aqueous phase drug concentration making them promising candidates for future propofol therapies.

1. Introduction

Propofol (2,6-diisopropylphenol), a common anesthetic, is formulated as an oil-in-water (O/W) emulsion and administered intravenously. One commercially-available formulation of propofol known as Diprivan® is prepared with 1% propofol dissolved in 10% soybean oil stabilized with 1.2% egg lecithin surfactant and 0.005% sodium EDTA as a preservative (all w/v) (Thompson and Goodale, 2000). Diprivan® has some disadvantages including thermodynamic instability, limited shelf life, risk of hypertriglycemia after injection (Baker and Naguib, 2005; Driscoll et al., 2002; Hulman, 1995; Knibbe et al., 2002). However, Diprivan® is most notable for causing significant patient pain on injection which is partially attributed to the free drug concentration (Baker and Naguib, 2005; Lee, 2010; Sim et al., 2009), or the portion of drug which dissolves in the emulsion aqueous phase. A more recent formulation known as Propofol Lipuro® has been observed to reduce the free drug concentration up to 30% (Yamakage et al., 2005) with an excipient oil mixture of 5% long-chain triglycerides (LCT) and 5% medium-chain triglycerides (MCT). Propofol Lipuro® is reported to have reduced incidence of pain on injection (Ozawa et al., 2005; Sundarathiti et al., 2007), but 37% of patients still reported pain after injection (Larsen et al., 2001). These observations suggest that pain on injection can be decreased by further decreasing the aqueous drug concentration of the propofol formulation.

The free drug concentration of an emulsion system is driven by its solubility equilibrium. Propofol is poorly soluble in water at 150–180 μg/mL (Altomare et al., 2003 Trapani et al., 1996). While a majority of the drug in Diprivan® is encapsulated in the oil phase, propofol concentrations in the aqueous phase have been observed as high as 14.8 μg/mL (Lee, 2010; Sim et al., 2009; Yamakage et al., 2005). After injection, the aqueous phase drug concentration makes immediate contact with the vasculature while the encapsulated drug must first diffuse out of the emulsion droplets. It is well established that sterically-hindered phenolic compounds such as propofol are biological membrane irritants (Hayashi et al., 1999), thus the drug in the emulsion aqueous phase can cause significant tissue irritation and damage. This hypothesis is supported by studies with propofol microemulsions which are a

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thermodynamically-stable subclass of emulsions with greatly reduced interfacial tension and droplet sizes (<100 nm) due to higher surfactant to oil ratios (Spernath and Aserin, 2006; Date and Nagarsenker, 2008; Bagwe et al., 2001; Li et al., 2012; Morey et al., 2006; Ryoo et al., 2005). Microemulsions were initially considered attractive candidates for propofol delivery, but poor results were seen with elevated pain levels on injection of microemulsion propofol (Hasani et al., 2012; Lee et al., 2011; Morey et al., 2006; Sim et al., 2009). Elevated pain with microemulsion propofol is attributed to greater aqueous phase drug concentration of 83.9 μg/mL (Sim et al., 2009).

Despite causing less pain on injection, macroemulsions (or simply emulsions) have limited shelf life and increased risk for complications after injection (Driscoll et al., 2002; Hulman, 1995). Emulsions are subject to several destabilizing mechanisms including gravimetric settling, flocculation, coalescence, Ostwald ripening, creaming, and finally phase separation each with unique driving forces and mechanisms. However, several strategies can be employed to increase emulsion stability. Smaller emulsion droplets are less susceptible to the more destructive mechanisms of creaming, settling, and phase separation (McClements, 2007). Nanoemulsions are a distinct classification of thermodynamically unstable emulsions which achieve kinetic stability when their droplet size is reduced with high shear mixing. Both commercial formulations of propofol listed above are classified as nanoemulsions.

In addition, excipient and surfactant selection also has strong effects on the resulting emulsion stability. Certain surfactants are more effective at stabilizing some oil compounds but have little effect on other oils. Some surfactants, for example the nonionic Pluronics, can provide strong rigidity to the emulsion interface resulting in minimal surface deformation during collisions between neighboring droplets (Gregory, 1995; Tadros, 2006). Electrostatics and DLVO theory suggest that electrostatic repulsion between droplets provides an energy barrier which deters neighboring droplets from approaching (Derjaguin and Landau, 1941; Verwey and Overbeek, 1948; Tadros, 2006). Additives can also be used to modify density or viscosity of each phase to resist gravimetric settling or reduce droplet collisions (McClements, 2007). Thus, there is a very broad scope of emulsion design, and it is challenging to design a shelf-stable emulsion.

Therefore, the goals of this study are to reduce the free drug concentration in propofol emulsion formulations while maintaining acceptable emulsion stability. We also investigate the dominant forces behind emulsion kinetic stability before finally presenting an improved propofol formulation.

2. Materials and methods

Propofol USP was donated by Albemarle Corporation (Baton Rouge, LA) and Diprivan® was kindly provided by Nanomedex, Inc. (Middleton, WI). Generally regarded as safe (GRAS) excipient oils including soybean oil, olive oil, ethyl butyrate, isopropyl myristate, isopropyl palmitate, and octanoic acid were all obtained from Fisher Scientific (Hampton, NH). Food grade extra virgin olive oil was purchased at the local Publix grocery store (Lakeland, FL). All oils were used as received. Dulbecco's phosphate buffered saline (PBS), sodium caprylate, Pluronic F68, Tween 80, and Brij 78 were obtained from Sigma–Aldrich (St. Louis, MO). Sodium stearate was obtained from Alfa Aesar (Ward Hill, MA).

2.1. Reducing the free propofol concentration in emulsions

2.1.1. Equilibrium partition coefficients in pure excipient oils

Partition coefficients of propofol in different oils were measured by first equilibrating a mixture of propofol, water, and oil with mass fractions f_{drug},f_{aq}, and f_{oil}, respectively, then measuring the concentration of propofol in the aqueous phase. The drug loading was kept constant at 1%, while oil loadings were chosen to be 5 or 15% (all w/w). Additional experiments were performed at 10% excipient oil loading for ethyl butyrate and soybean oil because of the major focus on these oils in this work. The mixtures of drug, oil, and water were vigorously mixed for three days under high magnetic stirring (900 rpm). Following mixing, 5 mL of each mixture was pipetted into a borosilicate test tube which was then placed into a polypropylene centrifuge tube. The samples were centrifuged for three cycles of 1 h each at about 3000 rpm. Both oil and aqueous samples were carefully collected without disturbing the interface and analyzed for propofol and excipient oil concentration using high performance liquid chromatography (HPLC, Waters Acquity). A 50% water and 50% acetonitrile (v/v) mobile phase was used at 1 mL/min flow. Propofol peaks eluted through the 4 μm C18 column at approximately 4.5 minutes. The partition coefficient was obtained from a mass balance, *i.e.*,

$$M_{drug} = V_{aq}c_f + KV_{oil}c_f \quad (1)$$

where K is the oil–water partition coefficient, c_f is the aqueous drug concentration, M_{drug}, V_{aq} and V_{oil} are the mass of oil and volumes of water and oil, respectively in the system. The mass balance yields the following equation for K:

$$K = \frac{f_{drug} - (f_{aq}c_f/\rho_{aq})}{f_{oil}c_f/\rho_{oil}} \quad (2)$$

where ρ_{aq} and ρ_{oil} are the densities of water and oil, respectively.

2.1.2. Validation of aqueous phase drug concentration in emulsions

The aqueous phase concentration of several emulsions was measured using a dialysis method. A volume of emulsion containing 10% w/w soybean oil, 1% propofol and between 1 and 5% Pluronic F68 surfactant was placed in a well-rinsed 12–14 kDa MWCO dialysis bag (Fisher Scientific). The dialysis bag was then suspended into isotonic dialysis media at a 5:1 ratio of dialysis media to emulsion (v/v). We used a solution of 2.25% (w/w) glycerol in DI water as dialysis media which matched the osmotic pressure of emulsion samples. Care was taken to ensure that the dialysis bags did not leak into the dialysis media. Samples were taken from the dialysate at several time intervals to obtain transient free drug concentration data, and a final free drug concentration was observed when equilibrium was reached. Dialysate samples were analyzed with HPLC using an identical method for propofol concentration.

2.1.3. Equilibrium drug partitioning in mixtures of excipient oils

An optimal emulsion design may include a mixture of excipient oils. If mixing is ideal, drug partitioning in oil mixtures can be estimated based on the partition coefficients of the drug in each oil type. To explore this, we measured the drug partitioning in binary mixtures of soybean oil and ethyl butyrate with 1% drug loading and 10% total excipient oil loading (w/w). The relative fractions of excipient oil were varied between 100% ethyl butyrate and 100% soybean oil. These experiments were also repeated by replacing soybean oil with olive oil. The same procedure used to measure equilibrium partitioning of single excipient oils was followed.

2.2. Evaluating the stability of emulsion formulations

2.2.1. Emulsion preparation

We prepared emulsions with 1% propofol USP, 10% of various GRAS oils (soybean oil, olive oil, ethyl butyrate, isopropyl myristate, isopropyl palmitate, and octanoic acid), various concentrations of