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Rapid dissolution of propofol emulsions under sink conditions

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ABSTRACT

Purpose: Pain accompanying intravenous injections of propofol is a major problem in anesthesia. Pain is ascribed to the interaction of propofol with the local vasculature and could be impacted by rapid dissolution of the emulsion formulation to release the drug. In this paper, we measure the dissolution of propofol emulsions including the commercial formulation Diprivan®.

Methods: We image the turbidity of blood protein sink solutions after emulsions are injected. The images are digitized, and the drug release times are estimated from the pixel intensity data for a range of starting emulsion droplet size. Drug release times are compared to a mechanistic model.

Results: After injection, pixel intensity or turbidity decreases due to reductions in emulsion droplet size. Drug release times can still be measured even if the emulsion does not completely dissolve such as with Diprivan®. Both pure propofol emulsions and Diprivan® release drug very rapidly (under five seconds). Reducing emulsion droplet size significantly increases the drug release rate. Drug release times observed are slightly longer than the model prediction likely due to imperfect mixing.

Conclusions: Drug release from emulsions occurs very rapidly after injection. This could be a contributing factor to pain on injection of propofol emulsions.

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1. Introduction

Propofol (2,6-diisopropylphenol) is a widely used intravenous anesthetic with estimated annual sales of $400 million in the U.S. alone (Federal Trade Commission, 2012). Many oil-based pharmaceuticals, propofol included are formulated as oil-in-water (O/W) emulsions. Propofol is typically emulsified with triglyceride lipids. The first formulation to reach market, Diprivan®, is prepared with 1% (w/v) propofol dissolved in 10% soybean oil (Thompson and Goodale, 2000). Diprivan® is stabilized with 1.2% egg lecithin surfactant and 0.005% sodium EDTA as a preservative. Despite their widespread use, propofol emulsions have several deficiencies including shelf stability concerns (Baker and Naguib, 2005; Driscoll et al., 2002) and a risk of embolism when combined with other anesthetics (Park et al., 2003). Prolonged usage has been linked to hypertriglycemia and propofol infusion syndrome (Baker and Naguib, 2005; Knibbe et al., 2002). Additionally, propofol injections are accompanied by a pain which is hypothesized to occur due to interaction of the drug with the local vasculature.

In attempts to improve the stability of propofol formulations and minimize the lipid loading, several studies have successfully formed thermodynamically-stable microemulsions of propofol without the need for soybean oil or lipids (Bagwe et al., 2001; Date and Nagarsenker, 2008; Li et al., 2012; Morey et al., 2006; Ryoo et al., 2005; Spernath and Aserin, 2006). Microemulsions are a subclass of emulsions with increased surfactant to oil ratios resulting in smaller droplet size and thermodynamic stability (Baker and Naguib, 2005; Ruckenstein, 1978). At ambient light conditions, the small droplet sizes of microemulsions (under 100 nm) do not scatter visible light; they appear as visually clear solutions. While propofol microemulsions will improve the shelf life stability of the drug formulation, these formulations have exhibited elevated levels of pain after injection which has limited their acceptance in markets (Lee et al., 2011; Hasani et al., 2013; Sim et al., 2009). Previous studies attributed the increase in pain to a significantly higher concentration of propofol in the microemulsion aqueous phase (Morey et al., 2006; Sim et al., 2009). The aqueous phase concentration of propofol in Diprivan® is reported as 12.4 μg/mL compared to 83.9 μg/mL in microemulsion, nearly 7 times larger than Diprivan® (Sim et al., 2009).

Propofol can be described as a sterically hindered phenol, and most molecules of this functionality irritate biological membranes (Hayashi et al., 1999). It is thus reasonable to expect that interaction of the vascular endothelial cells with propofol would cause toxicity and elicit a pain response. Propofol is present in two different phases in the emulsion formulations at equilibrium – the free drug dissolved in the aqueous phase and the fraction emulsified in the oil phase. In a

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microemulsion with only propofol as the oil phase, the free aqueous concentration would slightly exceed the solubility limit of the drug due to the very small radius of curvature, as given by the Kelvin equation (Skinner and Sambles, 1972). In a macroemulsion such as Diprivan®, the presence of additional excipient oil in the emulsion reduces the chemical potential of the propofol dissolved in the emulsion droplets, thereby reducing the free aqueous concentration at equilibrium. It is thus expected that the free propofol concentration in microemulsions would be larger than that in emulsions such as Diprivan®.

After an injection, as the formulation contacts the venous walls, the endothelial cells are directly exposed to the free concentration in the formulation or a slightly reduced value due to dilution with blood. It would thus seem important to minimize the free concentration in the formulation. However, it should also be noted that in any O/W emulsion or microemulsion formulation, the majority of the drug is loaded in the emulsified oil phase. Therefore, interaction of the drug loaded in the oil phase with the vasculature should also be considered. As the dose dilutes with blood or drug is taken up into endothelial cells, the free drug concentration is reduced and drug loaded in emulsified oil droplets must diffuse out to maintain equilibrium. Consequently, the rate of transport of propofol from the emulsion droplets to the continuous phase could be an important contributor to local toxicity and pain.

The goal of this study is to measure the dissolution rates of micro- and macroemulsions of propofol experimentally under sink conditions and compare the results with predictions from a mass-transfer model. While dissolution rates have been measured for various pharmaceutical formulations, it is difficult to measure the rates for soft nano-sized particles due to short dissolution times. Several common techniques such as dialysis or diffusion cells are not usable for measuring the rapid dissolution of sub-micron size emulsions because the diffusion across the dialysis membranes represents the rate limiting step (Washington, 1989; Chidambaram and Burgess, 1999; Henriksen et al., 1995; Araújo et al., 2011). While this issue has been raised in several studies, it is still not uncommon for researchers to use dialysis bags to quantify drug release from nano- or microparticles, perhaps due to the difficulties in accurately measuring the release dynamics by any other suitable method. A recent publication focused on this issue and proposed a new method for measuring rapid release by observing the change in solution pH driven by drug transport into solution. The transient pH was determined by adding indicator chemicals to the solution which change color with pH (Salmela and Washington, 2014). This method allows measuring drug release with fractions of a second resolution which is far superior to dialysis, centrifugation, diffusion cells, etc. Here we developed a simple optical technique based on imaging the emulsions after injection into sink conditions and quantifying the turbidity of the mixture by averaging the pixel intensity. Light scattering from a particle or droplet is proportional to the sixth power of the radius. This suggests a small change in radius due to drug dissolution will have a strong impact on the scattered light increasing sensitivity of the method. Since images can be taken at high frame rates with a standard digital camera, it is possible to obtain improved resolution with this method over other approaches. This method is limited to systems in which the droplet size changes due to drug loss, and may not be feasible for measuring release from solid particles. In this study, we use this optical method to measure drug release durations from emulsions of pure propofol and Diprivan® comparing the experimental results to a mass transfer model.

2. Materials and methods

Sodium chloride was obtained from Fisher Scientific (Hampton, NH). Surfactants used were Pluronic F68, Tween 80, and sodium caprylate, all obtained from Sigma–Aldrich (St. Louis, MO). Dehydrated bovine serum albumin (BSA) and Dulbecco's phosphate buffered saline (PBS) were also obtained from Sigma–Aldrich. Propofol USP and Diprivan® were donated by Nano-Medex Corporation (Middleton, WI). Soybean oil USP was obtained from Spectrum Chemical (Gardena, CA). All solutions were prepared by mass using a laboratory balance (Denver Instrument M-220D) and magnetically stirred. Surfactant solutions were prepared in either deionized (DI) water or PBS. BSA solutions were dissolved in PBS. All other compounds and materials were used as received.

2.1. Model

Consider the rapid mixing of a propofol emulsion into an aqueous solution with sufficient large volume or solubility to mimic perfect sink conditions. Prior to mixing, the free propofol concentration in the aqueous phase of the emulsion is in equilibrium with the oil phase. Mixing with the sink solution disturbs the equilibrium creating a driving force for propofol to dissolve and diffuse into the aqueous phase. We model the dissolution process of propofol emulsions by treating each droplet of the emulsion independently and assuming that the far field concentration for each droplet is approximately zero due to sink conditions. The concentration of propofol at the droplet boundary is in equilibrium with the emulsion droplets, which is influenced by the oil composition of the emulsified phase as well as the curvature and surface tension of the interface as given by the Kelvin equation (Buckton and Beezer, 1992; Wu and Nancollas, 1998; Sun et al., 2012; Hefter and Tomkins, 2003). Two cases were investigated in this study. The first case considers emulsions with an oil phase of only propofol such as in several proposed microemulsion formulations. The second case considers macroemulsions which contain soybean oil as an excipient such as the formulation Diprivan® used clinically.

2.1.1. Case 1 – pure propofol oil phase

Since the emulsified phase contains only propofol in this case and the surface tension of the surfactant covered droplets is small, we neglect the increase in solubility due to curvature and use the solubility limit in the aqueous phase at normal temperature and pressure as the equilibrium concentration. We also assume the surfactant at the interface is not a significant barrier to diffusion. Based on these assumptions, the rate of mass of the drug from the oil phase to the aqueous phase is given by the following equation

$$\frac{dm}{dt} = -\frac{D_{\mathrm{eff}} c_b^*}{\delta} A_s N \tag{1}$$

where m is the mass of propofol in the droplets, N is the total number of oil droplets in the system, D_{eff} is the effective diffusion coefficient of propofol in the aqueous phase, c_b^* is the equilibrium concentration, A_s is the surface area of a droplet, and δ is the diffusion boundary layer thickness. The boundary layer thickness varies based on the flow conditions and droplet size (Garner and Suckling, 1958). The relationship between boundary layer thickness and the size of a dissolving particle or droplet has been the subject of several studies (Bisrat and Nyström, 1988; Niebergall et al., 1963; Floyd et al., 1986; Lu et al., 1993; Wang and Flanagan, 2002), however, most of these studies consider significantly larger particle sizes. For the small droplet sizes investigated in this study (under 2000 nm), the Reynolds number is negligible, thus we the convection term can be neglected from convection–diffusion equation. Solving the convection–diffusion equation with pseudo-steady state conditions and the above assumptions gives a solution where the boundary layer thickness is equal to the droplet radius (Floyd et al., 1986).

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