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Optimizing surfactant content to improve oral bioavailability of ibuprofen in microemulsions: Just enough or more than enough?

Xiuhua You [a,1], Qiao Xing [a,1], Jue Tuo [a], Weijuan Song [a], Ying Zeng [b,**], Haiyan Hu [a,*]

[a] School of Pharmaceutical Sciences, Sun Yat-sen University, University Town, Guangzhou 510006, PR China
[b] Pharmacy Department of Guangdong General Hospital, Guangdong Academy of Medical Sciences, Guangzhou 510080, PR China

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ABSTRACT

Microemulsions show excellent potential as drug delivery systems, but the surfactants used to prepare them can cause side effects. Researchers have explored various strategies to expand microemulsion area and thereby reduce the surfactant content necessary, but how these strategies affect drug oral bioavailability has not been investigated in detail. Microemulsions were prepared using 16% or 24% mixed surfactant Tween 80-Cremophor EL-PEG400 (1:1:2) and either 6% caprylic/capric triglyceride oil (GTCC) or 6% or 15% mixed oil (Maisine™ 35-1 with GTCC). Some microemulsions contained just enough surfactant based on ternary phase diagrams, while others had excess surfactant. All empty and ibuprofen-loaded microemulsions were clear or translucent with a slight blue color, and they remained stable after dilution and centrifugation. In experiments with rats, oral bioavailability ($AUC_{0\rightarrow t}$) of ibuprofen in the microemulsions was similar for the different formulations (6779.0–7413.3 min μg/mL) and significantly higher than that of an ibuprofen suspension (4830.9 min μg/mL). The different formulations behaved similarly in a cellular uptake assay with Caco-2 cells. These results suggest that excess surfactant does not increase oral bioavailability or cellular uptake of ibuprofen. Therefore, to minimize side effects, using just enough surfactant to ensure microemulsion stability and drug solubility may be an appropriate strategy.

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1. Introduction

Microemulsions, which consist of surfactant, cosurfactant, oil and water, have attracted significant attention as drug delivery systems because of their thermodynamic stability, ability to solubilize hydrophobic drugs and ease of scale-up (Milan-Johann Schwuger, 1995; Moulik and Paul, 1998). In particular, studies have suggested that microemulsions can significantly improve the oral bioavailability of hydrophobic drugs by increasing their solubility (Kawakami et al., 2002b). This solubilization effect has been attributed largely to the ability of the surfactant to form either a drug-surfactant complex (Moreno et al., 2001) or strong hydrogen bonds with the drug (Tian et al., 2012). Surfactants in microemulsions can also enhance drug absorption by altering membrane fluidity or permeability of the gastrointestinal tract, as well as by blocking members of the multidrug resistance protein-associated family, including P-gp (Li et al., 2011; Lo, 2003; Peltier et al., 2006).

Several self-microemulsifying drug delivery systems include relatively high surfactant content (>20%), such as Sandimmun Neoral®, Norvirand® and Fortovase®, which may help explain why they provide higher drug bioavailability than the drug in solution (Gursoy and Benita, 2004). These high surfactant compositions also facilitate large-scale manufacture of the microemulsions.

The advantages of high surfactant levels come at a price, however, as they can cause serious toxic effects in cells, damage to the gastrointestinal mucosa, and allergic reactions (Buyukozturk et al., 2010; Constantinides, 1995; Kawakami et al., 2002a; Nornoo et al., 2009). This highlights the importance of optimizing the surfactant composition so that it is sufficient to ensure good oral bioavailability but below the levels associated with significant side effects. Such optimization requires detailed understanding of how surfactant composition affects oral bioavailability, cellular uptake, and safety, which is largely lacking in the microemulsion literature. Researchers have described several strategies for reducing the surfactant content, including the use of mixed oils and mixed surfactants (Chong-Kook Kim et al., 2001), but few studies have examined the functional consequences of these approaches.

* Corresponding author. Tel.: +86 20 3994 3118; fax: +86 20 3994 3118.
** Corresponding author. Tel.: +86 20 83827812x60250; fax: +86 20 83827812x60233.
E-mail addresses: zhaozengying@163.com (Y. Zeng), lsshhy@mail.sysu.edu.cn (H. Hu).
[1] These authors contributed equally to this work.

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Here we use ibuprofen-loaded microemulsions as a model system to examine the effects of different oil and surfactant compositions on the oral bioavailability in rats, as well as on the cellular uptake of the nanoparticles by Caco-2 cells. These cells are frequently used as a model for evaluating oral absorption of diverse drug formulations, including microemulsions (Gould et al., 2000) We prepared our microemulsions using Maisine™ 35-1 and GTCC as mixed oils to increase the microemulsion area, allowing us to experiment with different surfactant amounts. We tested microemulsions containing just enough surfactant, such that they lay near the phase transition point in the ternary phase diagram, and microemulsions containing excess surfactant, such that they lay far from the phase transition point.

2. Materials and methods

2.1. Materials

Ibuprofen (IBU) was provided by Hubei Biocause Pharmaceutical Co. (Hubei, China). Naproxen was purchased from the National Institute for Food and Drug Control (Beijing, China). Caprylic/capric triglyceride (GTCC) was a gift from Guangzhou Hanglian Chemical Industry Co. (Guangzhou, China). Glyceryl monolinoleate (Maisine™ 35-1), polyglyceryl oleate (CC497), oleoyl macrogolglycerides (LM1944CS), glyceryl monooleate PeceolÔ (GMO), glycerol monostearate GeleolÔ (GMS), Labrasol and Transcutol HP were gifts of Gattefoss (France). Ethyl oleate (EO) was purchased from Shanghai Feixiang Chemical Factory (Shanghai, China). Tween 80 and ethanol were purchased from Baishi Chemical Co. (Tianjin, China). Cremophor EL was from BASF (Germany). Polyethylene glycol (PEG) 400 was supplied by Fuchen Chemical Reagent Factory (Tianjin, China). Distilled water was prepared in-house and used for all formulations and dilutions.

2.2. Solubility studies

The solubility of ibuprofen was examined in various oils, surfactants and cosurfactants. In these experiments, excess ibuprofen was added to 2 mL of solvent in closed centrifuge tubes. These tubes were shaken on an orbital shaker at 25 °C at 100 rpm for 72 h to allow equilibration. Then the tubes were centrifuged at 21,000 × *g* for 5 min to separate soluble material from precipitate. Supernatants were diluted and analyzed by high-performance liquid chromatography (HPLC, Agilent 1200, Agilent Technology, USA) in order to determine the concentration of soluble ibuprofen. Solvents in which ibuprofen showed good or excellent solubility were chosen for preparing microemulsions.

2.3. Construction of phase diagrams

Pseudo-ternary phase diagrams were constructed using the water titration method at room temperature. First, surfactants or oils containing more than one component were mixed well to produce a homogeneous liquid; if necessary, gentle heating was applied during mixing. Next, surfactants were mixed with cosurfactants, surfactant-cosurfactant mixtures were blended with oils, and the resulting blends were titrated into distilled water dropwise under gentle stirring. The ratio of oils to surfactant-cosurfactant mixtures varied according to the materials being used. During titration, phase clarity and flowability were assessed visually. Transparent and translucent samples with low viscosity were considered to be microemulsions (Chen et al., 2004). No attempt was made to analyze other regions of the phase diagrams in detail.

2.4. Screening of surfactants, cosurfactants and oils

In order to minimize the surfactant content of our microemulsions, we favored the use of multi-component surfactants or oils, which led us to focus on blends that would increase microemulsion area. To help us select blends, we examined the percentage of microemulsion area in the pseudo-ternary phase diagram, as well as the percentage of microemulsion area in which the total content of surfactant-cosurfactant (S-Cos) was no more than 30%.

Based on our tests of ibuprofen solubility, Tween 80-Cremophor EL and Labrasol-Cremophor EL were chosen as the mixed surfactants, and PEG 400 and Transcutol HP as cosurfactants. In all cases, we ensured that these components would provide extensive microemulsion regions.

To further enlarge the microemulsion area, various oils were screened using Tween 80-Cremophor EL-PEG 400 (1:1:1, w/w/w) as a mixed surfactant system. These oils included GTCC, EO, Maisine™ 35-1 and LM1944CS on their own or together in mixtures.

In the final stage of formulation testing, we defined Tween 80-Cremophor EL (1:1) to be the mixed surfactant, PEG 400 to be the cosurfactant and GTCC-Maisine™ 35-1 (1:1, w/w) to be the oil phase. We mixed surfactant and cosurfactant in different weight ratios (Km) of 2:1, 1:1 and 1:2 and compared the resulting phase diagrams.

2.5. Preparation of microemulsions

Microemulsions with different compositions were prepared as indicated in Table 1 according to the following method. Maisine™ 35-1 was melted at 55 °C to allow easy mixing with GTCC. Then S-Cos mixtures were added to this oil phase and mixed. Distilled water was slowly added under continuous gentle stirring to yield microemulsions. To load the microemulsions with ibuprofen, the drug was dissolved in S-Cos-oil mixtures to a final concentration of 1% (w/w), then distilled water was added to obtain ibuprofen-loaded microemulsions.

Table 1
Appearance, droplet Size, zeta potential and conductivity of ibuprofen-loaded microemulsions.

Formulation	Composition				Appearance	Droplets		Conductivity (μS/cm)	Zeta potential (mV)
	Oil	Oil (%)	S-Cos (%)	Drug (%)		Size (nm)	PDI		
ME-A	GTCC	6	24[a]	1	Clear	24.70	0.105	150.67	−8.22
ME-B	GTCC-Maisine™ 35-1 (1:1)	6	24[b]	1	Clear	18.26	0.087	141.12	−5.46
ME-C	GTCC-Maisine™ 35-1 (1:1)	15	16[a]	1	Clear	34.82	0.104	120.33	−6.62

S-Cos Tween 80-Cremophor EL-PEG 400 (1:1:2).
[a] Surfactant content was just sufficient to form microemulsions.
[b] Surfactant content was more than necessary to form microemulsions.
Abbreviations: ME, microemulsion; PDI, polydispersity index; S-Cos, surfactant-cosurfactant mixture.

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