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Optimized mixed oils remarkably reduce the amount of surfactants in microemulsions without affecting oral bioavailability of ibuprofen by simultaneously enlarging microemulsion areas and enhancing drug solubility

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ABSTRACT

The toxicity and irritation associated with high amounts of surfactants restrict the extensive utilization of microemulsions. To address these shortcomings, employing mixed oils to enlarge microemulsion areas therefore reducing surfactant contents is a promising strategy. However, what kinds of mixed oils are more efficient in enlarging microemulsion areas still remains unclear. In this research, we found that the chain length and degree of unsaturation of oils play a key role in enlarging microemulsion areas. The combination of moderate chain saturated oil caprylic/capric triglyceride (GTCC) with long chain unsaturated oil glycerol trioleate significantly increased the microemulsion areas. Solubility of ibuprofen in the mixed oils was unexpectedly and remarkably increased (almost 300 mg/mL) compared with that (around 100 mg/mL) of the single oil (GTCC), which also resulted in greatly increased solubility of ibuprofen in mixed oils-containing microemulsions. By optimizing the mixed oil formulation, the absolute amount of surfactant in drug-loaded microemulsions was reduced but increased drug oral bioavailability in rats was maintained. It could be concluded that the combined use of moderate chain oils and long chain unsaturated oils could not only acquire enlarged microemulsion areas but also enhanced drug solubility, therefore doubly reducing surfactant amount, which is extremely beneficial for developing safe microemulsions.

1. Introduction

More than 40% of drug candidates discovered by high-throughput screening have poor solubility, which is one of the main reasons for failure in R&D due to impaired oral bioavailability (Lipinski et al., 2001). Great efforts have been made to improve the solubility of drug candidates. Among them, microemulsion achieves a dominant position owing to considerable solubilizing capacity to hydrophobic drugs, thermodynamical stability as well as easiness to scale-up. To date, however, only a few micro-emulsion products have been approved by the FDA. A disadvantage faced by microemulsion is that large amounts of surfactants are essential for the formation of microemulsion droplets and stabilization of latex particles during the process of polymerization and storage (Xu and Gan, 2005). Contradictorily, surfactants have potential toxicity such as hemolysis or histopathological alterations of the tissues so that the amount of surfactants controlled within a safe and reasonable range might be insufficient to form microemulsions (Swenson et al., 1994). A number of strategies have been developed to decrease the amount of surfactants in microemulsions. One approach is using mixed surfactants (Li et al., 2005; Moreno et al., 2003; Sun et al., 2014), which is effective in improving the solubilizing capacity of surfactants to enlarge microemulsion regions, hence reducing the amount of surfactants.

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Another is utilizing cosurfactants/cosolvents (Lawrence and Rees, 2000). As most cosurfactants/cosolvents are toxic medium- or short-chain alcohols themselves, they seldom contribute to the toxicity attenuation of microemulsions. Recently, using mixed oils has been demonstrated as a promising solution by our group and other researchers (Kim et al., 2001; You et al., 2014).

In previous studies, we proved that using mixed oils could remarkably reduce the amount of surfactants required in the preparation of microemulsions and excess surfactants would not be helpful to increase oral bioavailability of the encapsulated drug (You et al., 2014). However, to the best of our knowledge, no further investigation has been performed to show how to choose appropriate mixed oils to enlarge microemulsion regions. It was reported that medium chain triglycerides (MCT) possess higher fluidity and self-emulsification ability compared with long chain triglycerides (LCT), resulting in enlarged microemulsion regions (Charman et al., 1992; Shah et al., 1994). Furthermore, MCT also shows generally higher drug solubilizing capability than LCT, but no effort is made on the effect of carbon chain length of oils.

In this paper, by choosing a series of oils, we explored the influence of oil chain length, oil unsaturated degree and weight ratios of mixed oil on the microemulsion areas. To investigate the effect of mixed oils-containing microemulsions on drug oral bioavailabilities, ibuprofen (a BCS class II drug) was used as the model drug and the physiochemical characteristics and oral bioavailabilities of drug-loaded microemulsions with different oils and different amounts of surfactants were comparably evaluated.

2. Materials and methods

2.1. Materials

Ibuprofen was provided by Hubei Biocause Pharmaceutical Co., Ltd. (Hubei, China); naproxen was purchased from National Institute for Food and Drug Control (Beijing, China); caprylic/capric triglyceride (GTCC) and glycerol trioleate were presented by Guangzhou Hanglian Chemical Industry (Guangzhou, China); linoleic acid glyceride (Maisine™ 35-1), glyceryl monooleate (GMO) and glycerin monostearate (GMS) were from Gattefoss (France); ethyl oleate (EO), 1,2-propylene glycol, glyceryl tributyrate (tributyrin) and isopropyl myristate (IPM) were purchased from Shanghai Feixiang chemical factory (Shanghai, China); Tween 80 and ethanol were bought from Baishi chemical Co., Ltd. (Tianjin, China); Cremophor EL was presented by BASF (Germany); PEG 400 was supplied by Fuchen Chemical Reagent Factory (Tianjin, China). All other chemicals were of analytical grade. Distilled water, made in-house, was used for preparation of all solutions and dilutions.

2.2. Solubility

The solubility of ibuprofen in various oils and microemulsions was determined as follows: excess amount of ibuprofen was added to a sealed penicillin bottle containing 2 mL of vehicle. The bottle was shaken on an orbital shaker at 100 rpm for 72 h at 25 °C for equilibration, and then was allowed to stand still for 24 h at room temperature to avoid oversaturation. At the end of equilibration, the bottle was removed from the shaker and centrifuged at 17,000 × *g* for 5 min to separate drug precipitation. Subsequently, the obtained supernatant was diluted, and analyzed by HPLC (Agilent 1200, USA) to determine the concentration of ibuprofen (Li et al., 2014).

2.3. Construction of phase diagrams

To find the microemulsion formation areas and study the influence of oils of different chain length and unsaturated degrees on stable microemulsion areas, phase diagrams were constructed by water titration method at ambient temperature (25 °C) (Chen et al., 2004). Firstly, multi-composition surfactants and oils containing more than one component were well mixed. Heating was allowed during mixing if necessary. The surfactants were mixed with co-surfactants, and then surfactant-co-surfactant mixtures were blended with oils followed by titration with purified water dropwise under gentle stirring. Subsequently, the behavior of phase change was determined by visual inspection with the help of polarizing microscope (Ge et al., 2014). The single phase was signaled by the appearance of a clear, transparent, and homogeneous solution (Arpornpong et al., 2014).

2.4. The effect of mixed oils and co-surfactants on microemulsion areas

2.4.1. The effect of chain length and unsaturated degrees of oils

Tween 80–Cremophor EL–PEG 400 (1:1:2) was used as the surfactant system since it greatly enlarged microemulsion areas in our previous research (You et al., 2014). The percentages of microemulsion areas (MA) and the percentages of microemulsion areas with surfactant contents less than 30% (MA30) were employed to evaluate solubilizing capacity of oils or cosurfactants to form microemulsions in this paper.

Different chain length oils were mixed with Maisine™ 35-1, respectively as the oil phase. Among them, tributyrin was chosen as the short-chain oil, GTCC and IPM as the medium-chain oils, GMO and EO as the long-chain oils. Then we determined the effect of unsaturated degrees of oils by mixing them with GTCC such as GMS, GMO, EO, Maisine™ 35-1 and glycerol trioleate with various amounts of double bonds.

Table 1
Formulations, Droplet size, Zeta potential and Conductivity of different drug loaded MEs.

Code	Formulations					Appearance	Droplets		Conductivity (μs/cm)	Zeta potential (mV)
	Oil	Oil (%)	Stot (%)[a]	Drug (%)	Tween 80 (mg/10 mg)[b]		Size (nm)	PDI		
ME-A	GTCC	6	24	1	60	Clear	24.70	0.105	150.67	−8.22
ME-B	GTCC–glycerol trioleate (1:1)	6	24	1	60	Clear	28.78	0.114	703.01	−9.6
ME-C	GTCC–glycerol trioleate (1:1)	12	20	1	50	Clear	29.09	0.106	132.52	−3.6
ME-D	GTCC–glycerol trioleate (1:1)	12	20	2	25	Clear	30.73	0.128	217.56	−10.6
ME-E	GTCC–glycerol trioleate (1:1)	12	20	5	10	Clear	44.58	0.080	108.75	−3.4

[a] Stot, the total surfactants Tween 80–Cremophor EL–PEG 400 (1:1:2).
[b] The absolute amount of Tween 80 involved in drug-loaded microemulsions per 10 mg ibuprofen.

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