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Effect of ionization of drug on drug solubilization in SMEDDS prepared using Capmul MCM and caprylic acid

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ABSTRACT

The purpose of this study was to investigate the effect of ionization of drug on drug solubilization in SMEDDS (self-microemulsifying drug delivery system) prepared using Capmul MCM and caprylic acid. Solubilization capacity of blank SMEDDS dispersions for danazol, indomethacin and haloperidol as model drugs was determined. Based on the outcomes of solubilization capacity study, drug-loaded SMEDDS formulations were prepared and subjected to dispersion/precipitation study and droplet size analysis. Blank SMEDDS dispersions exhibited the highest solubilization capacity for haloperidol followed by indomethacin and danazol. Furthermore, the solubilization of the three drugs in blank SMEDDS dispersions was explained by a modified mathematical model. Dispersion/precipitation studies indicate that drug-loaded SMEDDS formulations exhibited superiority in solubilizing the drugs in comparison to their respective drug powder. In addition, indomethacin and haloperidol were found to reduce the droplet size of the microemulsions while danazol did not affect droplet size formation for drug-loaded SMEDDS formulations. These findings suggest that ionization of drug affects drug solubilization, droplet size formation, drug loading and drug dispersion/precipitation profiles for the SMEDDS formulations.

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1. Introduction

Poorly water-soluble drugs generally display low bioavailability due to poor aqueous solubility and dissolution rate [1]. For the development of oral dosage form products, the approaches to increase solubility or dissolution rate of these drugs for optimal bioavailability are needed [2]. Among several approaches reported in the literature, self-microemulsifying drug delivery system (SMEDDS) offers the potential for enhancing absorption...
and subsequently the better bioavailability of poorly water-soluble drugs by presenting the drug in solubilized form in the gastrointestinal tract [3–6]. SMEDDS is defined as an isotropic mixture of oils, surfactants/co-surfactants and drug, which rapidly forms microemulsion with droplet size typically less than 200 nm upon oral administration into the gastrointestinal tract [7–9]. The formed microemulsion enhances drug solubilization by incorporating the drug in lipid/surfactant colloidal aggregates formed upon contact with aqueous medium [10].

Depending on whether the drugs have ionizable groups or not, poorly water-soluble drugs can be roughly classified into pH-dependent (weak acidic/basic) and pH-independent (neutral) drugs [11]. Due to various degree of ionization of drug, the solubilization of the drugs in the lipid/surfactant colloidal aggregates may be different. Neutral drugs have been suggested to be solubilized in the lipid core while weak acidic/basic drugs have been suggested to be solubilized in the lipid core as well as at the surface of the colloidal aggregates due to their surface-active properties [10,12]. In contrast to neutral drugs which have less influence on the size and shape of the formed microstructures, weak acidic/basic drugs may change the size or shape of the microstructures by interacting with the surface of the microstructures [8,12]. It has been reported that phospholipid/isopropylmyristate mixture formed rod-like phospholipid/isopropylmyristate aggregates upon dispersion in water when no drug was loaded, while loading fenoprofen acid transformed the phospholipid/isopropylmyristate aggregates into spherical shape and loading fenoprofen sodium transformed the aggregates into extremely long rods [13]. Furthermore, the solubilization capacity for different drugs, upon dispersion of lipid/surfactant (and/or co-surfactant) systems (e.g., SMEDDS) in aqueous medium, is expected to be different due to various intermolecular forces between drug and SMEDDS components such as oils and surfactants/co-surfactants used.

In our previous study, SMEDDS based on medium-chain triglyceride “pre-digestion” products Capmul MCM and caprylic acid coupled with Cremophor RH40 as surfactant was successfully developed [14]. To further investigate the effect of ionization of drug on drug solubilization in the SMEDDS, danazol (MW 338), indomethacin (pKa 4.5, MW 358) and haloperidol (pKa 8.2, MW 376) were selected as the model drugs due to their difference in degree of ionization in aqueous medium but similarity in molecular weight/size. All three drugs belong to Biopharmaceutical Drug Classification System (BCS) Class II drugs which have poor aqueous solubility and high permeability [15]. Danazol is a synthetic steroid derived from ethisterone; it is a neutral drug with aqueous solubility of 0.42 μg/ml [16]. Danazol contains no acidic/basic group in its structure. Therefore, it does not ionize at any pH and its aqueous solubility is not affected by pH change. Indomethacin is a non-steroidal anti-inflammatory drug (NSAID) and is a weak acidic drug with the intrinsic aqueous solubility of 0.9 μg/ml [17,18]. Indomethacin contains a carboxyl group which ionizes at high pH and its aqueous solubility is highly pH dependent. Aqueous solubility of indomethacin increases dramatically when pH is higher than pKa (e.g., 630 μg/ml at pH 6.8). Haloperidol is a butyrophenone antipsychotic drug; it is a weak basic drug with the intrinsic aqueous solubility of 3.5 μg/ml [19,20]. Haloperidol contains a tertiary amine group which ionizes at low pH and therefore has pH-dependent solubility and exhibits high aqueous solubility at low pH (e.g., 1074 μg/ml at pH 1.2).

The SMEDDS studied in this investigation using Capmul MCM and caprylic acid was first applied to enhance solubilization of a neutral drug (i.e., danazol) [14]. To extend its application to non-neutral drugs, a weak acidic drug (indomethacin) and a weak basic drug (haloperidol) were used as the model drugs and compared with the results of using danazol reported from previous studies [14], with the purpose of addressing the effect of drug ionization on drug solubilization behavior upon dispersion of the SMEDDS in aqueous media at various pHs. Solubilization capacity, drug loading, drug dispersion/precipitation profiles and droplet size formation of either blank SMEDDS and/or drug-loaded SMEDDS of these three drugs were determined and compared. In addition, an attempt was made to evaluate and extend the application of a reported mathematical model to neutral, weak acidic and weak basic drugs in SMEDDS, which was initially proposed to explain solubilization of flurbiprofen in surfactant micelles [21]. This concept of attributing total drug solubilization to four drug-related species (D∞, D短期, D短期短期, D短期短期短期) provides a fundamental understanding of how drug ionization affects drug solubilization behavior upon dispersion of drug-loaded SMEDDS in aqueous media at various pHs.

2. Materials and methods

2.1. Materials

Capmul MCM (HLB 4.7) was obtained as a gift from Abitec Corporation (Columbus, OH). The composition of Capmul MCM is approximately 60% of medium-chain monoglycerides and 40% of diglycerides, derived from caprylic acid (83%) and capric acid (17%). Danazol was donated by Sanofi-Aventis Pharmaceutics (Bridgewater, NJ). Caprylic acid (HLB 1), indomethacin, haloperidol, hydrochloric acid (1 N), potassium chloride, potassium phosphate monobasic, sodium hydroxide, sodium acetate, acetic acid, and polyethylene glycol (PEG) 400 were purchased from VWR (Solon, OH). Cremophor RH40 (HLB 14–16) was supplied by BASF Corporation (Tarrytown, NJ). All chemicals and solvents were of analytical purity or high performance liquid chromatography (HPLC) grade and used as received with no further treatment.

2.2. Analytical methodology for danazol, indomethacin and haloperidol

Danazol samples were analyzed using a reversed-phase HPLC method modified from the literature [22]. The HPLC analysis system for danazol consisted of a Waters 600 controller, a Waters 717 plus autosampler and a Waters 2487 Dual λ detector. The chromatographic column was C18 Waters Symmetry column (3.5 μm, 250 mm × 4.6 mm). The mobile phase was a mixture of acetonitrile and distilled water (80:20, v/v) and the wavelength was 286 nm. The HPLC analysis system for indomethacin and haloperidol consisted of a quaternary pump, an autosampler and a diode array detector (HP1100 Series, Agilent
Table 1 – Composition of blank and drug-loaded SMEDDS formulations F5:5 and F4.5:4.5:1.

| Composition | Blank SMEDDS | Drug-loaded SMEDDS |
|-------------|--------------|-------------------|
| Formulation F5:5 | Capmul MCM:CA (1:1)* 50% | Danazol 50% |
|              | Cremophor RH40 50% | Indomethacin 50% |
|              | Drug 4.75 mg/g | Haloperidol 50% |
| Formulation F4.5:4.5:1 | Capmul MCM:CA (1:1)* 45% | Danazol 45% |
|              | Cremophor RH40 45% | Indomethacin 45% |
|              | PEG 400 10% | Haloperidol 45% |
|              | Drug 4 mg/g | 10% |
|              |               | 15.5 mg/g |
|              |               | 29 mg/g |

* Mixture of Capmul MCM and caprylic acid at the ratio of 1:1.

The composition of blank SMEDDS was selected based on the conclusion of phase diagrams reported elsewhere [14]. Two representative blank SMEDDS formulations were prepared and coded as blank F5:5 and F4.5:4.5:1 in this investigation. As listed in Table 1, blank F5:5 and F4.5:4.5:1 were composed of 50% and 45% Capmul MCM:CA (1:1) as lipid phase as well as 50% and 45% Cremophor RH40 as surfactant, respectively. In addition to the lipid and surfactant used, 10% PEG 400 as the co-surfactant was included in blank F4.5:4.5:1. The lipid phase was prepared by mixing Capmul MCM and caprylic acid (1:1 w/w) on a wrist-action shaker (Burrell Scientific, Pittsburgh, PA) at the highest speed (with the knob set at 10) for 48 h. The prepared lipid phase was filtered using 0.45 μm polypropylene filter and aliquots were diluted with the mobile phase for HPLC analysis of drug content.

2.4. Solubilization capacity study of blank SMEDDS for model drugs

Solubilization capacity of the blank SMEDDS dispersions for the model drugs was evaluated by determining the amount of model drugs solubilized in the blank SMEDDS dispersions. Therefore, equilibrium solubility of danazol, indomethacin or haloperidol in blank SMEDDS dispersions as a function of SMEDDS concentration was determined. Blank SMEDDS dispersions were obtained by dispersing 1, 2, 3, 4, or 5 g (0.4%, 0.8%, 1.2%, 1.6% or 2.0%, w/w) of blank SMEDDS into 250 ml of distilled water (pH 7.0), HCl buffer (pH 1.2), and phosphate buffer (pH 6.8), respectively, using USP apparatus II (paddle method) and the dispersion of blank SMEDDS was maintained at 37 °C using a water heater for 60 min with the paddle rotated at 50 rpm. The buffers were prepared as directed in the USP [25]. Thereafter, 5 ml of the resultant blank SMEDDS dispersions was taken and placed into a 20 ml scintillation vial. An excess amount of danazol, indomethacin or haloperidol was placed in the scintillation vial which was then shaken in a water bath shaker (New Brunswick Scientific, Edison, NJ) at 200 rpm and 37 °C for 48 h to achieve equilibrium solubility of the three drugs in the blank SMEDDS dispersions. The samples were filtered using a 0.45 μm polypropylene filter and aliquots were diluted with the mobile phase for HPLC analysis of drug content. In the case of haloperidol, following filtration, samples were diluted with a mixture of acetonitrile and 50 mM sodium acetate buffer (pH 3.5) (70:30, v/v) for HPLC analysis.

2.5. Preparation of drug-loaded SMEDDS

The excipient composition of drug-loaded SMEDDS formulations remained the same as blank SMEDDS formulations (blank F5:5 and F4.5:4.5:1). The amount of model drug (i.e., danazol, indomethacin or haloperidol) to be loaded was determined based on the outcomes of solubilization capacity studies. Drug-loaded SMEDDS formulations were prepared using the same preparation method of blank SMEDDS except that the model drugs were added into the resultant mixtures of blank SMEDDS before vortex and equilibration steps.
2.6. Dispersion/precipitation study of drug-loaded SMEDDS

Drug-loaded SMEDDS formulations were subjected to dispersion/precipitation study in distilled water (pH 7.0), HCl buffer (pH 1.2) and phosphate buffer (pH 6.8), respectively. The dispersion/precipitation study was performed using USP apparatus II (paddle method). One gram (~1 ml) of drug-loaded SMEDDS formulations was accurately weighed in a plastic weighing boat which was placed into the bottom of dissolution vessel, containing 250 ml of dispersion medium, using TDT-08 L Dissolution Tester (Pharma Alliance Group, Valencia, CA). The volume of 250 ml aqueous medium was used for dispersion study as per the solubility requirement of BCS [15]. The paddle speed was set at 50 rpm and the dispersion medium was maintained at 37 °C using a water heater. Samples (2 ml each) were withdrawn at 10, 20, 30, 60, 90 and 120 min for dispersion study in HCl buffer and up to 240 min in distilled water and phosphate buffer. The samples were processed and analyzed using the same methodology as described in solubilization capacity study. No replacement of fresh medium would dilute SMEDDS in the dispersion and potentially decrease its capability of maintaining the drug in the dispersion.

2.7. Droplet size analysis

A DelsaNano C particle size analyzer (Beckman Coulter Inc., Brea, CA) was used to measure the droplet size of the formed dispersions for drug-loaded SMEDDS formulations in various aqueous media. One gram of drug-loaded SMEDDS formulations was dispersed in 250 ml of distilled water (pH 7.0), HCl buffer (pH 1.2) or phosphate buffer (pH 6.8) using the same USP apparatus II setup as for obtaining blank SMEDDS dispersions to obtain drug-loaded SMEDDS dispersions. Approximately 2–3 ml of samples was taken for droplet size analysis. Blank SMEDDS dispersions formed in distilled water, HCl buffer and phosphate buffer were also prepared using the same USP apparatus II setup and droplet size was determined for comparison.

3. Results and discussion

3.1. Solubilization capacity study of blank SMEDDS for model drugs

Solubilization capacity of blank SMEDDS formulations for danazol, indomethacin and haloperidol upon dispersion in distilled water, HCl buffer and phosphate buffer, respectively, was determined. Danazol has an aqueous solubility of 0.42 µg/ml. Linear relationship between solubilization of danazol and SMEDDS concentration was observed in all three aqueous media for both blank F5:5 and F4.5:4.5:1 (Fig. 1). The solubilization of danazol for blank F5:5 and F4.5:4.5:1 increased to 35 ±1.2)–258 ±5.5 µg/ml and 32 ±1.8–222 ±3.8 µg/ml in distilled water, to 33 ±1.7–222 ±3.8 µg/ml and 30 ±1.5–204 ±5.9 µg/ml in HCl buffer, and to 19 ±1.2–154 ±4.8 µg/ml and 16 ±2.1)–149 ±5.0 µg/ml in phosphate buffer, respectively, when the concentrations of SMEDDS were increased from 0.4% to 2.0%.

Solubilization of indomethacin was found to have linear relationship with the SMEDDS concentration in distilled water and HCl buffer but not in phosphate buffer (Fig. 2). The intrinsic aqueous solubility of indomethacin for blank F5:5 and F4.5:4.5:1 was determined to be 0.9 µg/ml. The solubilization of indomethacin increased to 72 ±3.3)–541 ±15.1 µg/ml and 62 ±2.3)–448 ±9.0 µg/ml in distilled water, to 78 ±0.5)–454 ±18.8 µg/ml and 64 ±2.4)–446 ±3.3 µg/ml in HCl buffer, and to 548 ±13.6)–668 ±18.8 µg/ml and 512 ±5.4)–624 ±7.9 µg/ml in phosphate buffer, respectively, when the concentrations of SMEDDS were increased from 0.4% to 2.0%.

Solubilization of haloperidol was found to have linear relationship with SMEDDS concentration in distilled water and HCl buffer but not in phosphate buffer (Fig. 3). In comparison to its intrinsic aqueous solubility of 3.5 µg/ml, the solubilization of haloperidol for blank F5:5 and F4.5:4.5:1 increased to 1401 ±10)–5988 ±208 µg/ml and 1248 ±20)–5602 ±154 µg/ml in distilled water, to 1202 ±65)–1819 ±70 µg/ml and 1181 ±66)–1662 ±93 µg/ml in HCl buffer, and to 130 ±6)–4426 ±8 µg/ml and 116 ±1)–3890 ±67 µg/ml in phosphate buffer, respectively, when the concentrations of SMEDDS were increased from 0.4% to 2.0%.
3.2. Effect of ionization of drug on drug solubilization behavior in SMEDDS

The solubilization behavior of danazol, indomethacin and haloperidol in the same blank SMEDDS dispersion exhibited vast differences due to various degree of ionization of the three drugs. A mathematical model has been proposed in the literature to explain the solubilization behavior of a weak acidic drug, flurbiprofen, in pH-surfactant solutions [21]. In this model, the total solubilization of the drug is considered as the combined effects of pH and micellization. To better understand ionization of drug on drug solubilization behavior in SMEDDS, the published model was modified and utilized for all the three drugs. In this modified model, it is assumed that four drug-related species are considered to have contribution to the total solubilization of the drug (Fig. 4). $D_u$ and $D_i$ represent unionized and ionized drugs diffused out from drug-loaded SMEDDS and then solubilized in the aqueous medium upon dispersion of drug-loaded SMEDDS, respectively. $D_{u\text{-SMEDDS}}$ and $D_{i\text{-SMEDDS}}$ represent unionized and ionized drugs remained in the formed oil microdroplets upon dispersion of drug-loaded SMEDDS in the aqueous medium, respectively. Therefore, the total drug solubilization can be expressed as follows:

$$D_{\text{total}} = D_u + D_i + D_{u\text{-SMEDDS}} + D_{i\text{-SMEDDS}}$$  \hspace{1cm} (1)

For a neutral drug like danazol, no ionization of the drug was expected in the aqueous medium. The solubilization of the drug was contributed by $D_u$ and $D_{u\text{-SMEDDS}}$. Because danazol has a very poor aqueous solubility ($D_u$), solubilization of danazol in SMEDDS dispersions was essentially contributed by SMEDDS components and their concentrations ($D_{u\text{-SMEDDS}}$). As a result, linear relationship between solubilization and SMEDDS concentrations was observed in all aqueous media at various pHs. The solubilization enhancement in phosphate buffer was less pronounced than that observed in distilled water and HCl buffer. This could be due to the fact that high pH causes ionization of caprylic acid, leading to partial loss of hydrophobic components which results in lower solubilization capacity in phosphate buffer.

For a weak acidic drug like indomethacin, when in equilibrium, $D_u$ is the intrinsic aqueous solubility, and $D_i$ can be determined using following equation [11,26]:

$$D_i = D_u \cdot 10^{\text{-pK}_a}$$  \hspace{1cm} (2)

When the blank F5:5 and F4.5:4.5:1, regardless of the SMEDDS concentration used, were dispersed in distilled water, the pH of dispersions decreased to around 4 due to the acidity of caprylic acid. However, when the blank SMEDDS formulations were dispersed in HCl buffer, the pH of the dispersions remained 1.2 due to the buffering effect of HCl.
buffer. Because pKa of indomethacin is 4.5 and $D_u$ of indomethacin is small (0.9 $\mu$g/ml), $D_i$ was small at pH 4 and 1.2. Hence, the solubilization of indomethacin in distilled water and HCl buffer dispersions was predominantly attributed to the SMEDDS components and their respective concentrations ($D_u$-SMEDDS and $D_i$-SMEDDS). Therefore, similar linear solubilization profiles between drug solubilization and SMEDDS concentration were observed in distilled water and HCl buffer (Fig. 2). However, in phosphate buffer, solubilization of indomethacin was more complex because pH also plays an important role in its solubilization ($D_i$ and $D_i$-SMEDDS). A substantial increase in solubilization of indomethacin was observed at SMEDDS concentration of 0.4% due to the high pH of the dispersion (pH 6.6) and SMEDDS components. However, the dispersion of 0.8% of blank SMEDDS in phosphate buffer resulted in a dispersion having pH 6.4 due to the acidity of caprylic acid. Because the solubilization of indomethacin is sensitive to pH change at high pH range, the increase of indomethacin solubilization provided by increasing SMEDDS concentration from 0.4% to 0.8% was not enough to compensate for the decrease of solubilization due to the decrease of pH in the dispersions. Consequently, declines of indomethacin solubilization were observed. Thereafter, the dispersions of 1.2%–2.0% of blank SMEDDS formulations in phosphate buffer maintained pH around 6.4 due to buffering effect of phosphate buffer and association of caprylic acid at relatively high concentration. Consequently, $D_i$ remained unchanged and solubilization of the drug was mainly attributed to $D_u$-SMEDDS and $D_i$-SMEDDS but not the small $D_u$. As a result, indomethacin solubilization increased along with SMEDDS concentration increasing from 0.8% to 2.0%.

For a weak basic drug like haloperidol, when in equilibrium, $D_u$ is the intrinsic aqueous solubility and $D_i$ can be written as follows [11,26]:

$$D_i = D_u \cdot 10^{pK_a - p[H]} \quad (3)$$

As described previously, when the blank F5:5 and F4.5:4.5:1, regardless of the SMEDDS concentration used, were dispersed in distilled water and HCl buffer, the pH of dispersions remained around 4 and 1.2, respectively. Hence, $D_i$ remained constant and $D_u$ is constant. As a result, haloperidol solubilization increased linearly with SMEDDS concentration in distilled water and HCl buffer (Fig. 3). However, in phosphate buffer, the pH of dispersions was decreased to 6.6 at SMEDDS concentration of 0.4% and then maintained at 6.4 from 0.8% to 2.0%. $D_i$ was small at this pH range. Haloperidol solubilization was therefore predominantly attributed to $D_u$-SMEDDS and $D_i$-SMEDDS. Consequently, haloperidol solubilization increased along with the increase of SMEDDS concentration. Since caprylic acid ionizes to caprylate at high pH, the overall solubilization of haloperidol in phosphate buffer was less pronounced than that observed in distilled water. In addition to its direct effect on $D_i$ and $D_i$-SMEDDS, pH also indirectly affects hydrogen bond formation between weak acid and weak basic drug which has been suggested to be responsible for haloperidol solubilization [27]. In distilled water, in addition to pH and SMEDDS components, the hydrogen bond formation between caprylic acid and haloperidol contributes greatly for the pronounced solubilization enhancement. In HCl buffer, caprylic acid was predominantly protonated and less likely to form hydrogen bond with haloperidol. Therefore, a substantial increase was obtained at SMEDDS concentration of 0.4% due to pH effect. Thereafter, drug solubilization increases linearly with the SMEDDS concentration at a much slower rate. However, in phosphate buffer, caprylic acid was predominantly ionized to caprylate at SMEDDS concentration of 0.4% and hydrogen bond formation was not favorable; hence, less drug solubilization was observed. Thereafter, at SMEDDS concentrations from 0.8% to 2.0%, ionization of caprylic acid might be impeded due to buffering effect of the aqueous medium and association of SMEDDS components at high concentrations. Therefore, hy-

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Fig. 4 – Schematic representation of ionization of drug on drug solubilization upon dispersion of drug-loaded SMEDDS in aqueous media at various pHs ($D_u$ and $D_i$): unionized and ionized drugs diffused out from drug-loaded SMEDDS and then solubilized in the aqueous medium upon dispersion of drug-loaded SMEDDS; $D_u$-SMEDDS and $D_i$-SMEDDS: unionized and ionized drugs remained in the formed oil microdroplets upon dispersion of drug-loaded SMEDDS in aqueous medium).
hydrogen bond formation is progressively favored and consequently, more extensive drug solubilization enhancement was observed.

3.3. Preparation of drug-loaded SMEDDS

The composition of drug-loaded SMEDDS formulations was listed in Table 1. Drug loading was calculated based on the lowest solubilization capacity for each drug in blank SMEDDS dispersions. For example, one gram of blank F5:5 dispersed in phosphate buffer exhibited the lowest solubilization capacity for danazol at 19 μg/ml. Therefore, 4750 μg (19 μg/ml × 250 ml) or 4.75 mg danazol was loaded per gram of blank F5:5 for the preparation of danazol-loaded SMEDDS formulation F5:5. Similarly, 4 mg danazol was loaded per gram of blank F4.5:4.5:1. Using the same concept, the amounts of indomethacin to be loaded in blank SMEDDS formulations were calculated to be 18 mg/g and 15.5 mg/g for indomethacin-loaded F5:5 and F4.5:4.5:1, respectively. And, the amounts of haloperidol to be loaded were 32.5 mg/g and 29 mg/g for haloperidol-loaded F5:5 and F4.5:4.5:1, respectively.

Typically, the amount of drug to be loaded in blank SMEDDS formulations is based on drug solubility in individual excipients or in the mixtures of SMEDDS compositions (e.g., mixture of lipids and surfactants). The advantage of this method is to ensure that the drug is completely solubilized in the SMEDDS formulations [3]. However, drug solubilized in the SMEDDS formulations does not necessarily guarantee drug solubilized upon dispersion into aqueous medium. This is because hydrophilic excipients (e.g., surfactants, and/or co-solvent) contained in the SMEDDS formulations might lose some of solubilization capacity upon diluting with aqueous medium due to relocation of the hydrophilic molecules in the aqueous medium [3,28]. For example, extensive drug precipitation was observed upon dispersion of fenofibrate-loaded SMEDDS formulations in water, for which fenofibrate was loaded based on its solubility in the lipid components [28].

Therefore, to avoid any possible drug precipitation during dispersion/precipitation study, drug loading was not based on their solubility in the SMEDDS components but based on the lowest solubilization capacity provided by blank SMEDDS dispersions.

3.4. Dispersion/precipitation study of drug-loaded SMEDDS

All drug-loaded SMEDDS formulations, indomethacin powder and haloperidol powder except for danazol powder were dispersed in distilled water, HCl buffer and phosphate buffer to evaluate drug dispersion/precipitation profiles at various pH. Danazol-loaded SMEDDS formulations were dispersed in the three aqueous media because they contain caprylic acid and are subject to pH effect. Danazol powder was dispersed only in distilled water because it is pH independent. Overall, in comparison to their respective drug powder, the use of SMEDDS formulations significantly enhanced solubilization of danazol, indomethacin, and haloperidol.

For danazol-loaded F5:5 and F4.5:4.5:1 (Fig. 5), danazol remained dispersed and solubilized in all three aqueous media and no drug precipitation was observed up to 4 h. However, for danazol powder, very little or no drug solubilization was detected in distilled water.

For indomethacin-loaded F5:5 and F4.5:4.5:1 (Fig. 6), indomethacin was well dispersed and solubilized in all three aqueous media and no drug precipitation was observed up to 4 h. In contrast, indomethacin powder was poorly solubilized in distilled water (from 0.1 μg/ml to 5 μg/ml at 240 min) and HCl buffer (not detectable). Indomethacin powder was only well solubilized in phosphate buffer due to its high solubility at this pH (630 μg/ml).

Similarly, for haloperidol-loaded F5:5 and F4.5:4.5:1 (Fig. 7), haloperidol was well dispersed and solubilized in all three aqueous media and no drug precipitation was observed up to 4 h. On the other hand, haloperidol powder showed very poor solubilization in either distilled water (not detectable) or phosphate buffer (not detectable). Haloperidol powder only showed good solubilization in HCl buffer due to its high solubility at this pH (1074 μg/ml).

Despite the fact that the SMEDDS significantly enhanced solubilization of danazol, indomethacin and haloperidol during dispersion of drug-loaded SMEDDS, drug loading in SMEDDS...
formulations and the resultant dispersion/precipitation profiles of the three drugs exhibited vast differences. For formulation F5:5, drug loading was 4.75, 18 and 32.5 mg/g for danazol, indomethacin and haloperidol, respectively. For formulation F4.5:4.5:1, drug loading was 4, 15.5 and 29 mg/g for the three drugs, respectively. This is because drug loading was calculated based on solubilization of the three drugs provided by blank SMEDDS dispersions. As discussed above, the solubilization behavior of the drugs in blank SMEDDS dispersions was ascribed to ionization of the drugs. Non-ionizable neutral danazol exhibited much less pronounced drug solubilization enhancement than ionizable weak acidic/basic drugs (indomethacin and haloperidol). Correspondingly, drug loading was much lower for danazol than that of indomethacin and haloperidol in SMEDDS formulations. Similarly, dispersion/precipitation profiles were much less pronounced for danazol than that for indomethacin and haloperidol.

3.5. Droplet size analysis

The droplet size of the formed microemulsions upon dispersion of one gram of drug-loaded SMEDDS formulations in 250 ml distilled water, HCl buffer and phosphate buffer was determined and compared with the respective blank microemulsions. As outlined in Table 2, in comparison to the blank microemulsions, incorporation of danazol in the SMEDDS formulations did not significantly change the droplet size of the microemulsions. The droplet sizes of microemulsions from danazol-loaded F5:5 were 182, 177 and 60 nm in distilled water, HCl buffer and phosphate buffer, respectively, and are similar to 179, 175 and 64 nm for the corresponding blank microemulsions. In the case of danazol-loaded F4.5:4.5:1, 129, 147 and 36 nm were obtained for microemulsions in the three aqueous media, respectively, which are similar to 133, 155 and 33 nm for the corresponding blank microemulsions.

In contrast to danazol, loading indomethacin or haloperidol in the SMEDDS formulations was observed to reduce the droplet size of the formed microemulsions. For formulation F5:5, loading indomethacin or haloperidol resulted in microemulsions with droplet sizes of 83 nm and 79 nm or 93 nm and 102 nm in distilled water, HCl buffer and phosphate buffer, respectively, and are similar to 179, 175 and 64 nm for the corresponding blank microemulsions. Similarly, for formulation F4.5:4.5:1, loading indomethacin or haloperidol resulted in droplet sizes of 89 nm and 76 nm or 93 nm and 88 nm in distilled water and HCl buffer, respectively, which are smaller than 133 nm and 155 nm for the corresponding blank microemulsions. Interestingly, loading indomethacin or haloperidol did not appear to reduce the
droplet size of microemulsions formed in phosphate buffer. Droplet size of 55 nm or 76 nm was obtained for indomethacin- or haloperidol-loaded F5:5 microemulsions in comparison to 64 nm for the corresponding blank microemulsion. Similarly, droplet size of 33 nm or 45 nm was observed for indomethacin- or haloperidol-loaded F4.5:4.5:1 in comparison to 30 nm for the corresponding blank microemulsion.

The results of droplet size analysis indicate that ionization of drug might be one of the inducing factors for droplet size reduction of the microemulsions. Weak acidic or basic drugs are inherently surface-active reagents which influence phase behavior (e.g., droplet size and shape) of lipid/surfactant/water systems [10,12]. It has been suggested that solubilization of drugs changes the size or shape of the lipid/surfactant microstructures (e.g., microemulsions) only when the drug molecules are residing at the interface of the lipid/surfactant microstructures [10]. Therefore, no change in droplet size for danazol-loaded microemulsions indicates that solubilization of danazol mostly occurs in the lipid core but not at the interface of the formed microstructures. Moreover, the droplet size reduction observed for indomethacin- or haloperidol-loaded microemulsions suggests that solubilization of the drugs might be predominantly at the interface of the microemulsions. The solubilized drug molecules might intercalate into the interface of the microemulsions due to their surface-active properties, acting as co-surfactant to reduce the droplet size. In addition to drug effect, pH plays a major role in influencing the droplet size of microemulsions. As listed in Table 2, all blank or drug-loaded microemulsions formed in phosphate buffer exhibited much smaller droplet size than that of the microemulsions formed in distilled water and HCl buffer. At high pH, caprylic acid ionizes to caprylate which leads to reduced hydrophobic volume in the system. Also the resultant caprylate acts as co-surfactant to further reduce the droplet size of the microemulsions. Furthermore, pH effect might outweigh drug effect to reduce the droplet size small enough, leaving no space for drug effect. Consequently, no droplet size reduction was observed between drug-loaded microemulsions and the respective blank microemulsions in phosphate buffer.

4. Conclusion

The current investigation has explored the impact of ionization of drug, using danazol, indomethacin and haloperidol as model drugs, on drug solubilization in SMEDDS prepared using Capmul MCM and caprylic acid. The solubilization behavior of neutral, weak acidic and weak basic drugs in blank SMEDDS dispersions was evaluated using a modified mathematical model and the differences in drug solubilization were attributed to various degree of drug ionization. It was found that upon dispersion of drug-loaded SMEDDS in aqueous media at various pHs, four drug-related species (D_H, D_rounded, SMEDDS and D_rounded, SMEDDS) contribute to total drug solubilization. Correspondingly, drug loading and drug dispersion/precipitation profiles of drug-loaded SMEDDS for neutral, weak acidic and weak basic drugs also exhibited distinct differences. Furthermore, weak acidic/basic drugs but not neutral drugs reduced the droplet size of the microemulsions, indicating that ionization of drug also had significant impact on droplet size formation of the SMEDDS due to various intermolecular forces between the drugs and SMEDDS components.

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