Phase Manifestation and Formation of Nanoemulsions Composed of Imidazolium-based Ionic Liquid, Tween 80/Span 80 and Labrafac Lipophile WL 1349

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Ionic liquids (ILs) can enhance topical and transdermal delivery, as well as increase the solubility of sparingly soluble drugs. In the present work, pseudo-ternary phase diagrams of emulsions were composed of a mixture of non-ionic surfactants, polyoxyethylene sorbitan monooleate (Tween 80[®]) and sorbitan monooleate (Span 80[®]) in weight fraction: 1:1, 1:2, 2:1 and 2:3, Labrafac[™] Lipophile WL 1349 as an oil phase and 1-hexyl-3-methylimidazolium chloride [HMIM] (Cl)] as a continuous phase. Emulsion formulations were selected with 10% surfactants from the pseudo-ternary phase diagrams and further prepared at 298.2 ± 0.1 K. Acoustic emulsification method was used to prepare nanoemulsions that were mixed with freshly prepared hydrocolloid gum. The area of the single-phase zone in pseudo-ternary phase diagrams that varied with Tween 80[®]/Span 80[®] ratio in the order of $2:1 > 1:1 > 2:3 > 1:2$ where Span 80[®] was replaced by an equivalent weight of Tween 80[®] to form IL-based nanoemulsions. [HMIM] [Cl] tended to create a two-phase system. Addition of carbopol[®] ultrez 20 copolymer into the continuous phase of the formulations gave single-phase nanoemulsions with good stability. The mixture of surfactants with weight ratio of 1:2 (Tween 80[®]/Span 80[®]) showed a good stability with the smallest particle size and greater surface charges in the system. These ionic liquid-based nanoemulsions might have the potential in drug delivery systems.

Key words: Ionic liquid; pseudo-ternary phase diagram; Carbopol[®] ultrez 20 copolymer; particle size

During recent decades, a class of environmentally friendly solvents, ionic liquids (ILs), has received growing interest due to their fascinating and outstanding physicochemical properties. Generally, ionic liquids (ILs) consist of large inorganic anions paired with organic cations and are liquefied salts. Properties of ILs such as low combustibility, wide electrochemical window, excellent thermal stability, wide liquid regions and exhibit low vapor pressure (Eastoe *et al.*, 2005). On account of some of their peculiar properties, ILs can be

used as ‘green’ alternatives to volatile organic solvents for a wide range of applications (Eastoe *et al.* 2005).

In recent years, ILs has gained several interests for the use in pharmaceutical applications such as solubilization of poorly soluble drugs (Jaitely, Karatas & Florence 2008; Mizuuchi *et al.* 2008; Moniruzzaman *et al.* 2010). IL-based microemulsions has become an interesting topic (Qiu & Texter 2008) and has advantages such as they can

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dissolve hydrophilic and hydrophobic chemicals substances and thus widen the use of ILs. On the other hand, ILs also exhibits antimicrobial activity that can make them useful as formulation preservatives or active pharmaceutical ingredients (APIs) (Pernak, Sobaszkiewicz & Mirska 2003).

ILs have also been studied in classical colloid and surface chemistry because of its amphiphilic nature, and IL-based microemulsions are the most popular (Smirnova *et al.* 2009; Zech & Kunz 2011). The first IL-based microemulsion was reported by Gao *et al.* (2004) where an IL was used to replace water content (Zech *et al.* 2010). In the subsequent investigations, various kinds of IL-based microemulsions have been prepared (Zech *et al.* 2010; Harrar *et al.* 2011; Behera, Dahiya & Pandey 2007; Zhang *et al.* 2011; Cheng *et al.* 2007). In most of the studies on IL-based microemulsions, the IL, such as 1-butyl-3-methylimidazolium tetrafluoroborate (C_4mim) (BF_4), was used as a replacement for water (Gao *et al.* 2007; Gao *et al.* 2007). Nevertheless, some ILs may serve as an appropriate replacement for oil phase, such as 1-butyl-3-methylimidazolium hexafluorophosphate (C_4mim) (PF_6) (Gao *et al.* 2006; Behera, Malek & Pandey 2009). Long alkyl chain ILs can also be used as surfactants, which are named as surface-active ionic liquids (Zech *et al.* 2009; Govind *et al.* 2012).

Nanoemulsions are a type of emulsions with uniform, extremely small droplet size, in the range 20–200 nm (Solans *et al.* 2003), and are optically transparent. Nanoemulsions have gained several interests for the use in many different applications due to its low viscosity, high kinetic stability against creaming or sedimentation and a large interfacial area (Solans *et al.* 2003). Nanoemulsions are also known as an isotropic mixture of natural or synthetic oils with surfactants and co-surfactants that form fine oil-in-water (O/W) or water-in-oil (W/O) with the droplet size usually below 500 nm (Solans *et al.* 2003).

The main objectives of this work are construction of pseudo-ternary phase diagrams and fabricate imidazolium-based IL nanoemulsions. In the design of the imidazolium-based IL nanoemulsions, 1-hexyl-3-methylimidazolium chloride [(HMIM) (Cl)] was chosen as the hydrophilic IL. The pseudo-ternary IL/Tween 80[®]-Span 80[®]/oil system consisted of IL stabilized by a mixture of two nonionic surfactants, polyoxyethylene sorbitan monooleate (Tween 80[®]) and sorbitan monooleate (Span 80[®]) in Labrafac[™] Lipophile WL 1349. In this study, Tween 80[®] and Span 80[®] surfactants were selected because the mixture of these surfactants offer many advantages over ionic surfactants including increased stability, formulating flexibility and wider compatibility. In addition, Tween 80[®] has hydrophilic PEO groups, which have a strong affinity with the imidazolium cation attached in ILs (Lu & Rhodes 2000). Dynamic light scattering (DLS) and zeta potential have been used to characterize the nanoemulsion systems.

MATERIALS AND METHODS

Materials

The ionic liquid (IL) used was hydrophilic 1-hexyl-3-methylimidazolium chloride [(HMIM) (Cl)] from Sigma-Aldrich Chemical Co. US. Polyoxyethylene sorbitan monooleate (Tween 80[®]) and sorbitan monooleate (Span 80[®]) were used as the hydrophilic and hydrophobic emulsifier, respectively and were purchased from Sigma-Aldrich Chemical Co. US. The oil used was Labrafac[™] Lipophile WL 1349 and was purchased from Gattefosse, France. The thickening agent used was Carbopol[®] Ultrez 20 copolymer from Lubrizol, USA.

Methods

Pseudo-ternary Phase Diagrams of the Emulsions. Labrafac[™] Lipophile WL 1349 with surfactants (Tween 80[®]/Span 80[®]) mixture at various weights ranging from 0:100 to 100:0 were weighed. A total weight of 0.5 g mixture

was placed in a 10 ml screw-cap glass tube, subjected to vortex for 30 min, and then stored at 298.2 ± 0.1 K overnight. An approximately 0.1% by weight of IL was added to the samples and homogenized for 2 min using a vortex mixer. Next, the samples were centrifuged for 15 min at 4000 rpm. Cross-polarized light was used to visually examine the phase changes of the samples for the determination of anisotropic and isotropic regions. The different phase regions were then classified into isotropic (L), two-phase (T) or three-phase (T_1). Mixtures of Tween 80® and Span 80® with the following ratios in weight fraction: 1:1, 1:2, 2:1 and 2:3 were used to study the phase behaviour.

Emulsions Compositions from Pseudo-ternary Phase Diagrams

Composition of the selected emulsions preparation comprised of 10% surfactants from the pseudo-ternary phase diagram. The selections of dispersed and continuous phases of the present phase diagrams comprised 30% (w/w) Labrafac™ Lipophile WL 1349 and 60% (w/w) IL, respectively. Carbopol® Ultrez 20 copolymer was added in the continuous phase other than IL as a thickening agent.

Emulsions Preparation

An emulsion of selected composition from pseudo-ternary phase diagrams was prepared through acoustic emulsification method. A hydrocolloid gum, carbopol® ultrez 20 copolymer, was dispersed in deionized water at 2% (w/w) and then stored overnight. Ultrasonicator (UP400S Hielscher Sonifier, Germany) of 400 W nominal power and a frequency of 24 kHz equipped with a 22 mm sonotrode tip was used to prepare emulsions. The system was placed in a custom-built cooling jacket where chilled water passed through the jacket continuously at 3°C. An emulsion sample was prepared and homogenized for 5 min at 6000 rpm with a polytron® homogenizer (Kinematica GmbH, Germany) rotor stator. The sample was then further homogenized using

ultrasonic cavitation for 5 min. The sonifier tip horn was adjusted to 3 cm below the surface of a 100 ml sample. Ultrasonic cavitation was performed at the acoustic amplitude of 20% and 0.5 cycles. All samples were kept at room temperature, 298.2 ± 0.1 K.

Particle Size Measurements of the Emulsions

DLS technique utilizing a Malvern Zetasizer light scattering instrument (Malvern, UK) was used to determine the mean droplet size and size distribution by diluting one drop of the emulsion system with 10 ml of an aqueous phase containing deionized water. After the emulsion samples had been equilibrated for 24 h, the samples were filtered to remove dust or contaminants. Measurements were performed at $T = 298.2 \pm 0.1$ K.

Zeta Potential Measurements of the Emulsions

Zetasizer Nano (Malvern Instruments, UK) was used to perform zeta potential analysis. Zeta potential values either above or below ± 30 mV are usually stable emulsions without any coalescence and flocculation of the droplets in the system. Each sample was analyzed thrice, and each analysis consisted of five replicates.

RESULTS AND DISCUSSION

Pseudo-ternary Phase Diagrams of the Emulsions

Phase behaviour provides an essential clue to macroscopic behaviour, as it is an important factor in the thermodynamic characterization of the system. In addition, phase behaviour is an intimate way to express molecular or particle or inter-aggregate interactions on a monocular level. The basic principle is to mix the components and observe the number and nature of the phases (Pillai & Shah 1996). Phase diagrams are shown to provide valuable information on the role played by structures of

the polar phase, non-polar phase and surfactant in determining the properties of the system at any composition. As usually stated, regions of the emulsion could be characterized by ternary phase diagrams. Here, Tween 80[®]/Span 80[®] were used as the surfactants, and imidazolium IL of 1-hexyl-3-methylimidazolium chloride [(HMIM) (Cl)] and Labrafac[®] Lipophile WL 1349 were selected as the water and oil phase, respectively.

The transition from turbidity to transparency was observed to determine the phase boundaries. The liquid + liquid equilibrium phase diagrams

of HMIM Cl/Tween 80[®]-Span 80[®]/Labrafac[™] Lipophile WL 1349 at $T = 298.2 \pm 0.1$ K were investigated. Figures 1 (a), (b), (c) and (d), respectively represented the phase diagrams of three-components system with Tween 80[®]/Span 80[®] ratios, 1:1, 1:2, 2:1 and 2:3. A large amount of IL can be solubilized in the systems with a mixture of two surfactants. Nonionic surfactants in the presence of a second surfactant can dissolve water or oil to form o/w or w/o emulsions (Porras *et al.* 2008; Kunieda, Nakano & Akimaru 1995). This is because the second surfactant reduces interfacial tension of the system.

Figure 1. Pseudo-ternary phase diagram of the HMIM Cl/Tween 80[®]-Span 80[®]/Labrafac[™] Lipophile WL 1349 three component systems at $T = (298.2 \pm 0.1)$ K where L = isotropic region, T = two-phase region, T₁ = three-phase region. The weight ratio of Tween 80[®]/Span 80[®] (w/w): (a) 1:1; (b) 1:2; (c) 2:1 and (d) 2:3.

The phase diagram of HMIM Cl/Tween 80[®]-Span 80/Labrafac[™] Lipophile WL 1349 systems is shown in Figure 1. A one-phase region was observed, consisted an isotropic region (L) with the Tween 80[®]/Span 80[®] ratio in the order of 2:1 > 1:1 > 2:3 > 1:2, which indicated that the formation of IL-based emulsions where Span 80[®] was replaced by an equivalent weight of Tween 80[®]. By comparing the results from previous studies (Gao *et al.* 2006; Chakrabarty *et al.* 2005) with the results obtained in Figure 1, a large amount of IL can be solubilized in emulsions using much lower weight fractions of the mixture of Tween 80[®] and Span 80[®] surfactants. These can be explained in terms of interfacial properties provided by the mixtures of two different nonionic surfactants that are more favourable. Isotropic emulsions systems significantly affect the effectiveness as a delivery vehicle and shelf life.

In region T (two-phase region) and T₁ (three-phase region), phase separation occurred in a larger area where phase equilibria were not observed and emulsions were unstable. Two-phase region was dominant at most parts of the compositions that showed instability and incapability of the surfactant to work in emulsifying Labrafac[™] Lipophile WL 1349. Phase separation was observed for most ratios of imidazolium IL, HMIM Cl in emulsions containing less than 5% Labrafac[™] Lipophile WL 1349, with the sample prepared formed insoluble aggregates that remained at the bottom of the screw-cap glass tube and with a cloudy layer at the top.

Emulsions Compositions from Pseudo-ternary Phase Diagrams

An emulsion of selected composition from pseudo-ternary phase diagrams comprised of 30% (w/w) disperse phase, 10% (w/w) surfactants and 60% (w/w) continuous phase. Surfactants mixture of 10% (w/w) of Tween 80[®] and Span 80[®] with ratios: 1:1, 1:2, 2:1 and 2:3 were used to avoid

or minimize any adverse toxicological or dermatological effect. To determine the stability of the system, hydrocolloid gum, carbopol[®] ultrex 20 copolymer [2% (w/w)] was added into the continuous phase as a thickening agent. Hydrocolloid gum gave a single-phase with good stability to the emulsions system. Hydrocolloid gum increased the viscosity of the continuous phase that surrounds the oil droplets and therefore restricting the movement of particles. The high droplet concentration enhanced the stability of the emulsions as their movements were blocked by each other (McClements 1999). Thus, this slowed down the creaming rate, followed by the destabilization of emulsion.

Particle Size Measurements

The sizes and size distribution of colloidal dispersions were characterized by DLS method. A sample was irradiated with a laser beam and the resulting intensity of the scattered light produced by the particles fluctuates at a rate that was dependent upon the particles size. Nonionic surfactant weight ratio varying from 1:1, 1:2, 2:1 and 2:3 were studied. A series of samples were chosen from the pseudo-ternary phase diagrams for formulation and further studied using DLS method at different surfactants mixture ratio compositions. Figure 2 shows the particle size distribution plots that appear as S-shaped curve for four emulsions.

From the particle size distribution plots, it showed that the particle sizes with the cumulative distribution of 50% are the median droplet diameter. Nanoemulsion with weight ratio of Tween 80[®]/Span 80[®] (w/w) of 1:2 had a very small distribution with 50% of the particles under 176 nm compared to the emulsion with weight ratio of Tween 80[®]/Span 80[®] (w/w) of 2:3, 2:1 and 1:1, with 50% of the particles under 191 nm, 319 nm and 550 nm, respectively. The results demonstrated that for the dispersions system containing higher concentration of Span 80[®] with weight ratio of Tween 80[®] /

Figure 2. Cumulative particle size distribution at $T = (298.2 \pm 0.1)$ K of 10% (w/w) surfactants. The weight ratio of Tween 80[®]/Span 80[®] (w/w): 1:2, 2:3, 2:1 and 1:1.

Span 80[®] (w/w) of 1:2 and 2:3, the particle size decreased progressively. This observation can be explained as a result of increasing surfactant adsorption around oil interface of a droplet, and decreasing interfacial tension in the system, which favours the formation of nanoemulsions with smaller particle sizes (Lamaallam *et al.* 2005). It was observed that for the addition of Tween 80[®] concentration, there was an obvious shift of the plotted curves into the range of larger particle sizes. With higher surfactant concentration of Tween 80[®], the emulsions system leads to larger interfacial areas and consequently resulted in large particle sizes.

An addition of a co-surfactant to the emulsions is well known to alter their parameters. By using a standard practice of two different surfactants, it can develop an emulsion with optimal long-term stability and better steric stabilization of the droplets. Smaller droplet sizes with greater long-term stability can be observed by the addition of imidazolium cations to the formulation that can change the arrangement of the surfactants on the surface of oil droplets (Bataller *et al.* 2004).

Zeta Potential Measurements

Figure 3 shows the zeta potential for emulsions at room temperature. Zeta potential for the emulsions was in the range of -45.70 mV to -51.60 mV with the addition of carbopol[®] ultrez 20 copolymer. The surface charges of emulsions with weight ratio of Tween 80[®] / Span 80[®] (w/w), 1:2, 2:3, 2:1 and 1:1 were -51.60 , -50.10 , -48.30 and -45.70 mV, respectively. Zeta potential that gives a value of greater than or less than 25 mV indicates deflocculated and flocculated emulsions, respectively (Leiberman, Reiger & Banker 1989). Therefore, no flocculation is observed in all prepared emulsions. The stability of an emulsion can be improved with an increase in the surface charge (Liu *et al.* 2006).

The distribution of ions in the surrounding interfacial region could be affected by the development of a net charge at the particle surface. An electric double layer around each particle would be formed by increasing the concentration of ions of opposite charge to that of the particle close to the surface. Particles tend to repel each other and there was no

Figure 3. The zeta potential of emulsions at $T = (298.2 \pm 0.1) \text{ K}$ of 2% (w/w) hydrocolloid gum. The weight ratio of Tween 80®/Span 80® (w/w): 1:2, 2:3, 2:1 and 1:1.

observation of flocculation if all the particles had a large negative or positive zeta potential. The negative charged surface is due to the dissociation of acidic groups on the surface of a particle (Kuznesof & Whitehouse 2005). The imidazolium IL, HMIM Cl, in emulsions contained cations and anions, which have contributed to the negative charge on the surface.

CONCLUSIONS

The present study indicated that the classic O/W emulsions containing hydrophilic imidazolium IL, HMIM Cl were prepared. HMIM Cl was used to replace the water phase and was successfully incorporated into the formulation. DLS was used to estimate the droplet size of selected formulations and exhibited droplet size between the ranges of 176 nm to 550 nm. Zeta potential for emulsions with carbopol® ultrez 20 copolymer were found between the ranges of -45.70 mV to -51.60 mV . The increase in hydrophobic emulsifier concentration resulted in the reduced emulsion particle size. IL-based nanoemulsions were successfully formulated by a mixture of nonionic surfactants where strong tendency

of the surfactant head groups to bind with IL through the hydrogen bonding with weight ratio of Tween 80®/Span 80® (w/w), 1:2 and 2:3. IL-based nanoemulsions might have the potential as a drug delivery system.

LIST OF ABBREVIATIONS

h	hour
HMIM Cl	1-hexyl-3-methylimidazolium chloride
K	kelvin
ml	milliliter
mV	millivolt
nm	nanometer
O/W	oil-in-water
rpm	revolutions per minute
w/w	weight per weight

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