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Effect of a model lipophilic compound on the phase behaviour of hydrophilic self-micro-emulsifying lipid formulations

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ABSTRACT

Background: There has been growing interest in the self-emulsifying lipid technology in recent years as an approach to improve the oral bioavailability of poorly water-soluble compounds. Nonetheless, for the design of successful lipid formulations with a potential to maximize the bioavailability of lipophilic drugs, key elements in the lipid composite in relation to the physicochemical state of drug after dispersion needs to be optimized. **Methods:** In this study, various lipid formulations were optimized for oil-in-water micro-emulsion drug delivery systems. The effect of Ibuprofen (a model lipophilic drug) on the emulsification behavior of these systems was also investigated by constructing ternary phase equilibrium diagrams using dynamic phase behavior study method. **Results and Discussion:** Optimum self-micro-emulsifying systems were obtained by using oil blends of {Miglyol 812/Imwitor 308} at ratio of 5:5 in the case of Cremophor RH40 and 4:6 for Tagat S2 or Tagat S Ternary phase equilibrium diagrams reveal extended regions of L_2 phase when no drug was added to the lipid mixtures. However, in the case of lipid formulations containing Ibuprofen at 100mg/g, small limited areas of L_2 phase was observed which suggests that the drug can interfere in the mechanistic processes of emulsification. **Conclusion:** In order to design successful self-micro-emulsifying lipid systems, pre-formulation studies which affect the performance of resultant dispersions of these systems with and without drug should be carried using suitable emulsification media.

KEY WORDS: SMEDDS; SEDDS; Phase behavior studies; Poorly water-soluble drugs; Cremophor RH40

1. INTRODUCTION

There has been growing interest in the field of self-emulsifying lipid technology in recent years as an approach to improve the oral bioavailability of poorly water-soluble compounds. After the advent of Neoral® (Cyclosporine A,immunosuppressive agent) in 1995 by Novartis, Sandoze back then, lipid-based delivery systems have gained considerable research attention. Hence, many pharmaceutical products using SEDDS or SMEDDS were introduced to the market including,Targretin® (Bexarotene, Ligand), Norvir® (Ritonavir, Abbott), Agenerase®(Amprenavir, GlaxoSmithKline), Rocaltrol® (Calcitriol, Roche), Aptivus® (Tipranavite, BoehringerIngelheim), Lipirex® (Fenofibrate, Sanofi-Aventis)[1-3] and Avodart®(Dutasteride, GlaxoSmithKline)[4].

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SEDDS (Self-emulsifying drug delivery systems) are isotropic mixtures of oils (triglycerides), and/ or co-surfactant (mixed glycerides) and non-ionic surfactants which upon gentle agitation spontaneously emulsify in water producing fine oil in water (o/w) dispersionsof droplets <5µm[5]. On the other hand, Self-micro-emulsifying drug delivery systems (SMEDDS) contain in the lipid mix hydrophilic components such as, hydrophilic surfactants (HLB >12) and/ or hydrophilic co-solvents systemswhich when mixed with water under gentle agitation can produce an almost clear o/w microemulsion of oil droplets with diameters between 5 and 140nm[6]. These systems,based on various physicochemical factors such as; the hydrophilicity of the oil mixture, particle size of the resultant dispersion and the formulation digestibility were classified into type I, II, III and IV[7-8]. Hydrophilicity of the lipid mixture increases by moving from type 1 lipid class system to type 4. An archetypal example of a Type III system is the reformulation of cyclosporine A as Neoral®[9]. Type IV formulations do not contain natural lipids and represent the most hydrophilic formulations. An example of a Type

IV formulation is the current capsule formulation of the HIV protease inhibitor amprenavir (Agenerase®) which contains TPGS as a surfactant and PEG 400 and propylene glycol as co-solvents[10]. There is an obvious trend amongst formulation scientists to opt for Type IV class formulations as these systems have high solubilization capacity to drugs. Yet, due to hydrophilic nature of Type IV lipid class carriers may render lipophilic drugs susceptible to crystallization in the GIT lumen after dispersion, as these carriers tend to lose their solvent capacity during emulsification process. Dynamic of drug precipitation from the various types of lipid class systems highlighting the role of oil (source triglyceride and/or mono-diglycerides) in the lipid matrix in preventing drug crystallization after dispersion in the aqueous media was thoroughly investigated by Hasan et al[11-12].

Nonetheless, for the design of successful lipid formulations with a potential to maximize the bioavailability of lipophilic drugs, key elements in the lipid composite in relation to the physicochemical state of drug after dispersion needs to be optimized[13]. This process includes; determination of drug solubility in the lipid matrix, controlling factors which influence the hydrophilicity of the lipid vehicle such as type of oil, oil-cosurfactant ratio, type of surfactant and the inclusion of hydrophilic co-solvent. Also, it is important to investigate the effect of drug on the emulsification performance of these systems in suitable media simulating the physiological conditions of the GI tract. In this study, various lipid formulations were optimized for oil-in-water micro-emulsion drug delivery systems. The effect of Ibuprofen (a model lipophilic drug) on the emulsification behavior of these systems was also investigated by conducting phase behavior studies.

2. MATERIALS AND METHODS

2.1. Materials

Miglyol 812, medium chain triglyceride, (C_8/C_{10} mono/diglycerides) and Imwitor 308 were supplied by CondeaChemie GmbH. Tagat S2(PEG-(20)-glyceryl stearate) and Tagat S(PEG-(30)-glyceryl stearate)were supplied by Goldschmidt AG, Germany. The fatty acid distribution in Miglyol 812 according to the manufacturer is: caprylic (C_8): 50-65%, capric (C_{10}): 30-45%, caproic (C_6):<2% and Lauric acid C_{12}: <3%. Imwitor 308 is approximately a 9:1 mixture of C_8/C_{10} mono/diglycerides with 1% free glycerol. Cremophor RH 40 (PEG-(40)-hydrogenated castor oil) and Ibuprofen were supplied by BASAF as a gift.Simulated Gastric Fluid (SGF) without pepcin; 2.4g NaCl and 7ml HCl/1000ml water. All water used was Mili Q water.

2.2. Methods

2.2.1. Miscibility profiles for lipid mixtures

Regions of mutual miscibility of various lipidformulations containingvarious surfactants thatrepresent different HLB values were determinedusing ternary phase diagrams. Miscibility diagrams ofMiglyol 812 (source oil), Imwitor 308 (co-surfactant) and various surfactants including; Cremophor RH 40,Tagat S2 and Tagat S were constructed.Formulations of two grams which represent variouspercentages of oils, co-surfactants and surfactants onthe ternary phase diagrams were weighed in 20 mlglass test tubes and then tops were wrapped withcling film. Mixtures were placed in a water bath at 50ºC for 2 minutes before lipid components werethoroughly vortexed. Mixtures were then kept for 24-48 hours in an oven set up at 25°C before visualassessment. Samples that displayed two or more phases weredescribed as immiscible systems. Mixtures which formed a continuoussingle phase were classified as miscible formulations.

2.2.2. Self-Emulsification profiles of lipid mixtures

Mixtures of oils, co-surfactants andsurfactants were accurately weighed into glass test tubes and then wrapped bycling film followed by votrexing. Test tubes were held at 50°C in a thermostated water bath held for 2 minute before lipid mixtures were thoroughly vortexed. Lipid formulations were then left toequilibrate over night in an oven set up at 25°C. Emulsions were prepared under conditions of gentleagitation at a controlled temperature of 37°C. Anamount of 1g of each lipid mixture was introducedinto either 100ml of distilled water or media simulating gastrointestinal fluids (SGF) in a 500-ml glass beaker. Emulsification was carried out under agitation simulating *in vivo* situation. Agitation was provided by gentleshaking on a mechanical shaker at 100 oscillationsper min for 15 minutes. Visual assessment ofresulting dispersions was carried out and systemswhich produced clear micro-emulsions wereidentified as SMEDDS while milky turbid emulsions were denoted as SEDDS.

2.2.3. Phase behavior Study

Phase behavior study was carried out using dynamic method. Pseudo-ternary diagrams were constructed by blending oil mixtures of {Miglyol 812/Imwitor 308} at ratios of 5:5 or 4:6 with increasing concentrations (10-90% w/w) of either Cremophor RH40 or Tagat S2, respectively. Demineralized water was then sequentially added at

5% w/w intervals into the oil mixture under agitation. Systems were then allowed to equilibrate at 37°C for few minutes. The addition of water was continued until phase change was observed. Phases were identified as isotropic L_2 (oil-based liquids) or L_1 (aqueous-based liquids), liquid crystalline phases (LC) and multiphasic turbid mixtures (L_1+L_2). The phase behavior was also carried out in lipid mixtures containing Ibuprofen at 100mg/g.

3. RESULTS AND DISCUSSION

3.1. Effect of surfactants hydrophilicity on emulsification behavior of lipid systems

For the design of successful lipid formulations, three key constituents must be optimized which include; type of oil, co-surfactant and surfactant. There is a consensus amongst researchers[11,14-19] that the use of MCT as source of oil in SEDDS or SMEDDS enhances emulsification process of these systems as opposed to using LCT. Nonetheless, this does not preclude the importance of using LCT in the lipid composite in enhancing bioavailability of highly lipophilic drugs of log P> 5; as in the case of probucoal[20] and danazol[21]. Co-surfactants are considered polar oils generally composed of medium chain mono- and diglyceridescontaining small proportions of un-esterified glycerol. Co-surfactants with high monoglyceride content such as Imwitor 308, 312 and 191 have high HLB values (i.e. more polar) and may form liquid crystalline states which render them more susceptible to the ionic strength and temperature of the medium. It is thought that co-surfactants can stabilize the interface by penetrating into the void spaces among surfactant molecules in the surfactant film around the oil droplet and hence lowering the interfacial tension and increasing the interfacial fluidity[13]. Nonionic surfactants are normally used in oral self-emulsifying lipid. Emulsification efficiency of surfactants is verily controlled by the average HLB value and the empirical chemical structure of the surfactant. Polyoxyethylene hydrogenated caster oil derivatives have relatively shown relativelyhigher solubilization capacity to the oil composite and emulsification efficiency during aqueous dispersion.

Figure 1 shows the emulsification profile of blends composed of Miglyol 812 (source of oil), Imwitor 308 (co-surfactant) and Cremophor RH40 (non-ionic surfactant). Extended area of SMEDDS was observed which suggests the robustness of this lipid composite at minimal concentrations of surfactants. Optimum self-micro-emulsifying systems were obtained by using oil blends of {Miglyol 812/Imwitor 308} at ratio of 5:5 at Cremophor RH40 concentration of 20% w/w, see line AB depicted on figure 1. On the other hand, replacing Cremophor RH40 in the lipid mix with either Tagat S2 (figure 2) or Tagat S (figure 3) though has produced good SMEDDS area yet, still relatively less than SMEDDS area which is observed in the case of lipid mix containing Cremophor RH40. Furthermore, Optimum self-micro-emulsifying systems were obtained by using oil blends of {Miglyol 812/Imwitor 308} at ratio of 4:6 at Tagat S2 or Tagat S concentrationsof 30% w/w, see linen AB depicted on figures2 and 3. This suggests that the emulsification performance of lipid composites containing Cremophor RH40 is relatively better than using Tagat S2 or Tagat S in the oil mi. This might be due to variations in the HLB values and packing parameters of these non-ionic surfactants.The molecular packing parameter P_c is defined as v_o/al_o, where v_o and l_o are the volume and the length of the surfactant tail and a is the surface area per molecule. The expected aggregate shapes in relation to surfactant critical packing parameter are as follows; $0 \leq v_o/al_o \leq 1/3$ for sphere, $1/3 \leq v_o/al_o \leq 1/2$ for cylinder, and $1/2 \leq v_o/al_o \leq 1$ for bilayer[22]. Chemical structure of Cremophor RH40 exhibits triple-tailed surfactant molecule while Tagat S or S2 is single-tailed, see figure 4 for chemical structures. This suggests that Cremophor RH40 has relatively high P_c values(0.5 - 1) in comparison to either Tagat S or S2 (> 0.5). Therefore, Cremophor RH40 would possibly form flexible bilayer aggregates while in the case of Tagat S or S2 spherical or cylindrical aggregates are favored.

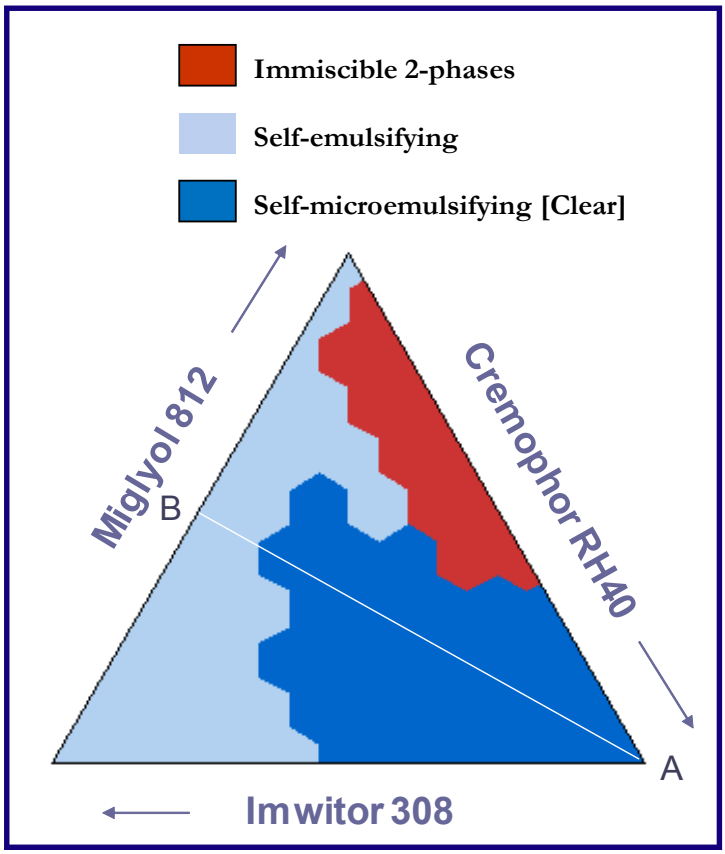

Figure 1: Ternary phase diagram of Miglyol 812/Imwitor 308-Cremphor RH40 depicting various areas of emulsification performance of representative oil mixtures. 1 g of each mixture was introduced into100ml of Milli-Q water and emulsified at 37°C for 15 minutes by gentle agitation. Line A-B represents formulations of {Miglyol/Imwitor} at ratio of 5:5 with increasing concentration of Cremophor.

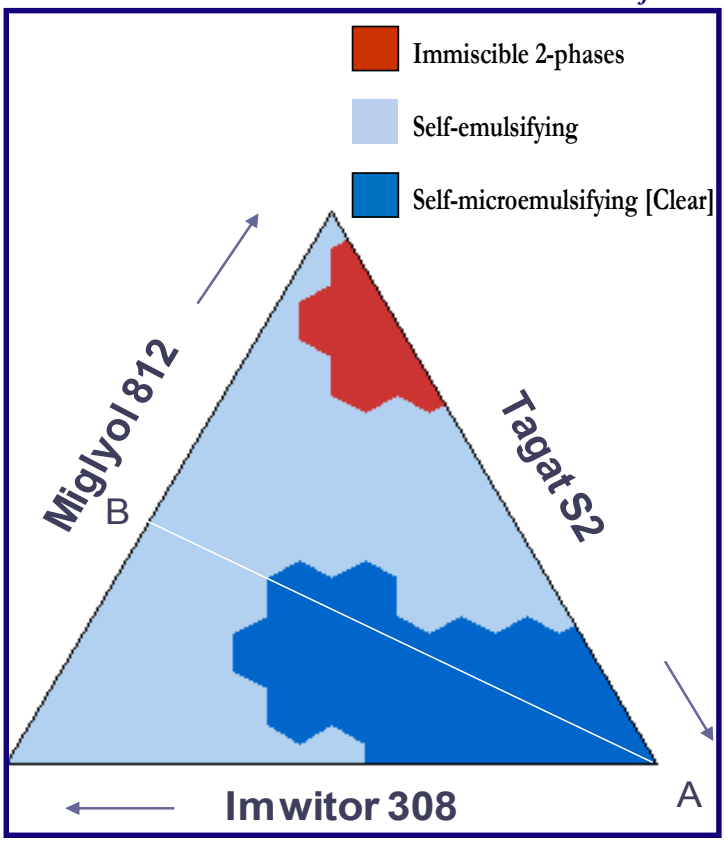

Figure 2: Ternary phase diagram of Miglyol 812/Imwitor 308-TagatS2 depicting various areas of emulsification performance of representative oil mixtures. Line A-B represents formulations of {Miglyol/Imwitor} at ratio of 4:6 with increasing concentration of Tagat S2.

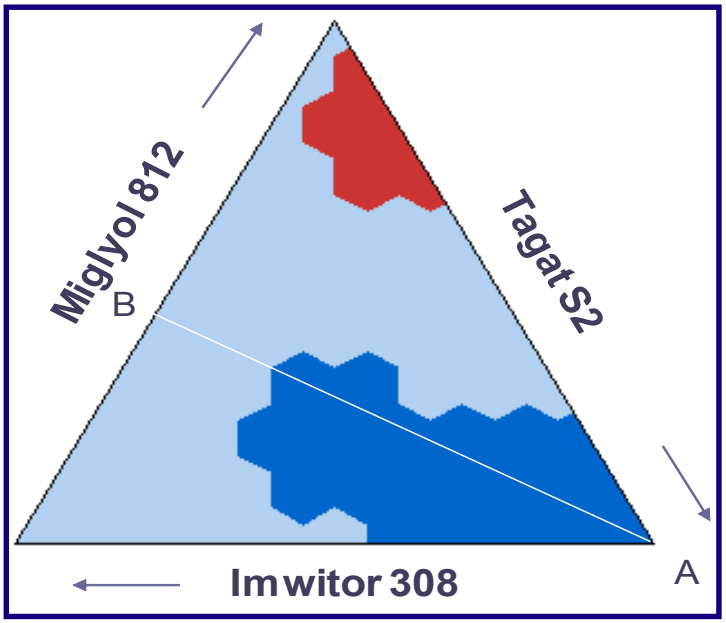

Figure 3: Ternary phase diagram of Miglyol 812/Imwitor 308-Tagat S depicting various areas of emulsification performance of representative oil mixtures. Line A-B represents formulations of {Miglyol/Imwitor} at ratio of 4:6 with increasing concentration of Tagat S.

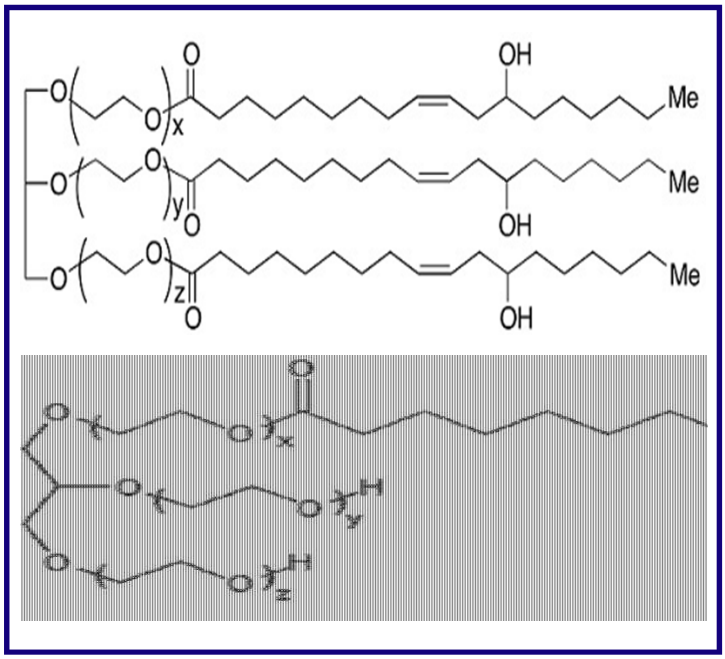

Figure 4: Chemical structures of (a) Cremophor RH40 (PEG-(40)-hydrogenated castor oil); x + y + z = 40 (b) Tagat S2 or S (PEG-(20/30) glycerol stearate; x + y + z = 20 or 30.

3.2. Effect of medium ionic strength on the emulsification behavior of lipid systems

The luminal environment in the proximal GI tract varies considerably with site and meal ingestion. Hence, it is essential to consider the use of several different sets of emulsification conditions to evaluate the dissolution behavior of the oil formulations with and without drugs. The United States Pharmacopoeia[23] denotes Simulated Gastric Fluid (SGF) to simulate dissolution in the stomach. SGF simulates pH conditions in the fasted stomach.

Generally, electrolytes present in the emulsification media, as the variation in temperature, can affect emulsification performance of lipid formulations. The preferential aqueous solubility of the surfactant is shifted to the oil phase due to salting out effect and thus inducing phase separation. This effect, however, can be averted by using surfactants with relatively high HLB values. Any reduction of the surfactant hydrophilicity incurred by electrolytes will not be sufficient to induce phase separation.The self-emulsifying system initially investigated by Pouton[16,24] which is composed of Tween 85-Miglyol 812 was shown to be influenced by the electrolytes present in the emulsification media. On the other hand, the Tagat TO-Miglyol 812 system produced by Wakerly[25-26],was shown to be capable of forming submicron emulsions with no effect of the medium ionic strength on the self-emulsification process. This resistance to the salting out effect of electrolytes present in the emulsification media is probably due to the fact that the non-ionic surfactant Tagat TO has a relatively higher HLB value than Tween 85, or due to the chemistry variations of the two aforementioned surfactants.

Furthermore, the self-micro-emulsifying system developed by Hasan[13] which is composed of Miglyol 812-Imwitor 988-Tagat To was susceptible to the effect of the electrolytes present in the emulsification media. As Imwitor 988 is polar oil, it causes depressions in phase inversion temperature PIT and also lossof surfactant's affinity for the aqueous phase due to electrolytes present in the media. This can induce phase separation and thus significant increase in droplet diameter[13]. This is clearly illustrated in table 1 which shows the effect of ionic strength of dispersion media (SGF versus water) on the emulsification behavior of various lipid mixtures, containing non-ionic surfactants with varying degree of hydrophilicity. In the case of lipid mixtures containing Cremophor RH40 (HLB 14-16) or, Tagat S (HLB 16.4), the emulsification performance has shown high resistance to the effect of temperature or electrolytes present in the emulsification media vis clear micro-emulsionswere obtained after dispersion in either water or SGF media at all surfactant concentrations. On the contrary, for formulations containing Tagat S2 (HLB 15), ionic strength of the media has dramatically influenced emulsification performance. Emulsification of lipid mixtures containing 30 to 40% w/w Tagat S2 in SGF media has produced turbid emulsionsin comparison to the optically clear dispersions in water. This effect, however, was retarded in the case of using Tagat S2 at higher concentrations of e" 50 %w/w. Therefore, it is essential to use sufficient amount of surfactants with relatively high HLB values in order to avert salting out effect of electrolytes present in the emulsification media. In this case, any reduction of the surfactant hydrophilicity incurred by electrolytes will not be sufficient to induce phase separation.

Table 1: The effect of emulsification media on the emulsification performance of various lipid mixtures.SGF: Simulated Gastric Fluid, EM: Emulsion (turbid dispersion) and ME: Microemulsion (optically clear dispersion).

Surfactant Concentration	30%		40%		50%	
Lipid Formulations	Resultant dispersion in various media					
	Water	SGF	Water	SGF	Water	SGF
{Miglyol/Imwitor} {5/5} / Cremophor RH40	ME	ME	ME	ME	ME	ME
{Miglyol/Imwitor} {4/6} / Tagat S	ME	ME	ME	ME	ME	ME
{Miglyol/Imwitor} {4/6} / Tagat S2	ME	EM	ME	EM	ME	ME

3.3. Effect of a model lipophilic drug on the phase behavior of lipid systems

In the design of successful lipid formulation with maximum drug absorption, the effect of the drug on the emulsification process has to be investigated. The exact physical state of the drug during the various stages of the emulsification process has to be highlighted using static or dynamic phase behavior methods. The mechanistics of self-micro-emulsifying lipid formulations after aqueous dispersion involve the following dynamic intermediate phases; L_2 phase (clear w/o micro-emulsion) → $L_1 + L_2$ phase (turbid emulsion phase) → L_C (liquid crystalline phase) → L_1 phase (clear w/o micro-emulsion). Depending on the hydrophilicity of oil mix, amount of co-surfactant and surfactant, $L_1 + L_2$ or L_c phase might not appear on the phase behavior map and thus the initial L_2 phase could pass through L_1 phase on progressive dilution with water. The former rout of emulsification might be quintessential for the bioavailability enhancement of highly lipophilic drug such as Danazol (Log P 4.5).The formation of turbid emulsion phase ($L_1 + L_2$ phase) throughout emulsification process may prevent crystallization of drug in the lumen of the gut as the drug will be sequestered in the oil phase minimizing direct contact with external aqueous phase. Another important factor which improves bioavailability of highly lipophilic drugs is the use of lipids composed of long-chain triglycerides (LCT). LCT stimulates the formation of lipoproteins, which facilitates their lymphatic transport[27]. On the other hand, the dynamic transformation from L_2 →L_1 phase without passing through intermediatory phases on progressive dilution with watermight be essential for bioavailability enhancement of intermediate lipophilic drugs of log P $\leq$ 2.5 such as Ibuprofen.

Figures 5 and 7 depict 3D representation of the equilibrium phases resulting from the progressive dilution of water of lipid system composed of either {Miglyol 812/Imwitor 308} (5:5)-CremophorRH40 or {Miglyol 812/Imwitor 308} (4:6)-Tagat S2, respectively. At least 20 % w/w of Cremophor RH40 (Fig 5) or 30 % w/w of Tagat S2 (Fig 7) is needed in the lipid mix to produce o/w microemlusion. On the hand, at least 40% w/w of either Cremophor RH40 or Tagat S2 is required to obtain all the way through clear dispersions (L_2 → L_1) on the progressive addition of water. Nonetheless, the inclusion of Ibuprofen at 100mg/g lipid has transformed phase behavior map on interaction with water for both systems as shown in figures 6 and 8. In comparison to the lipid systems without drug (Fig 5 and 7), small limited areas of L_2 phase was observed, see figures 6 and 8. Besides, the appearance of new intermediate phases L1+L2 and/or LC phases resulting from the progressive dilution with water before final clear o/w microemlusion is obtained.This suggests that the drug can interfere in the mechanistic processes of emulsification by blocking charge transfer during dispersion of the formulation. On the hand, at least 50% w/w of either Cremophor RH40 or Tagat S2 is needed respectively in both systems (Figs 6 and 8) for LC intermediate phases to appear

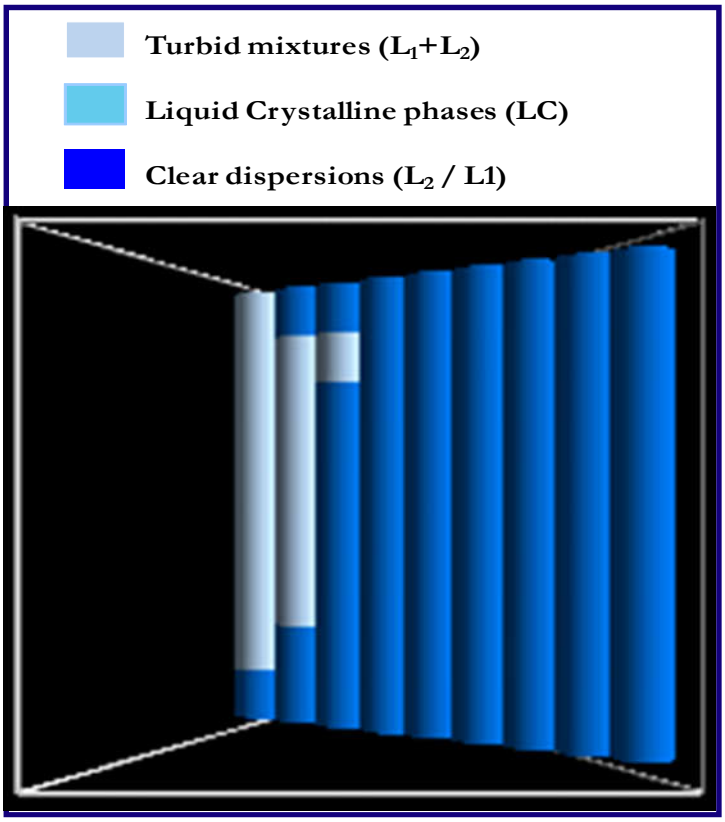

Figure 5: 3D representation of the equilibrium phase behaviour for {Miglyol 812/Imwitor 308} (5:5)-CremophorRH40 with no drug resulting from the incremental addition of water.

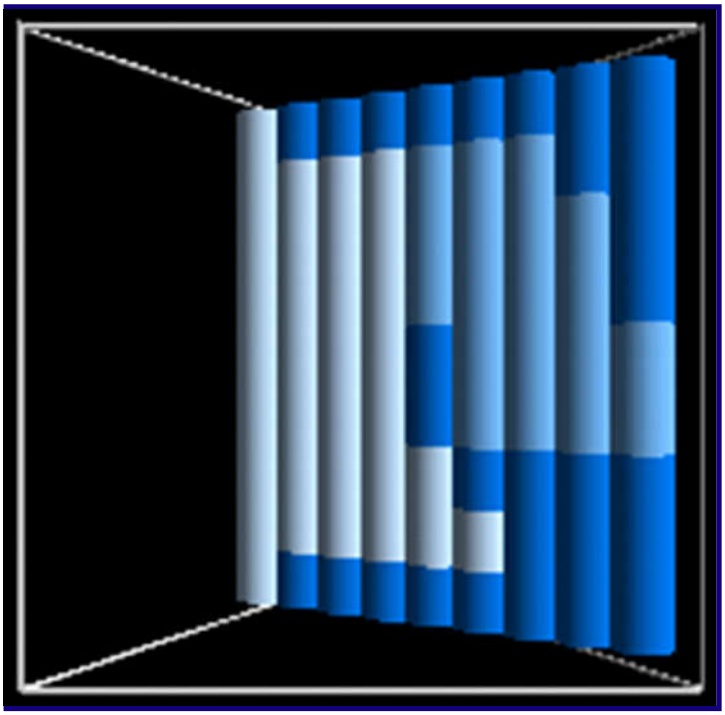

Figure 6: 3D representation of the equilibrium phase behaviour for {Miglyol 812/Imwitor 308} (5:5)-Cremophor RH40 with 10% Ibuprofen resulting from the incremental addition of water.

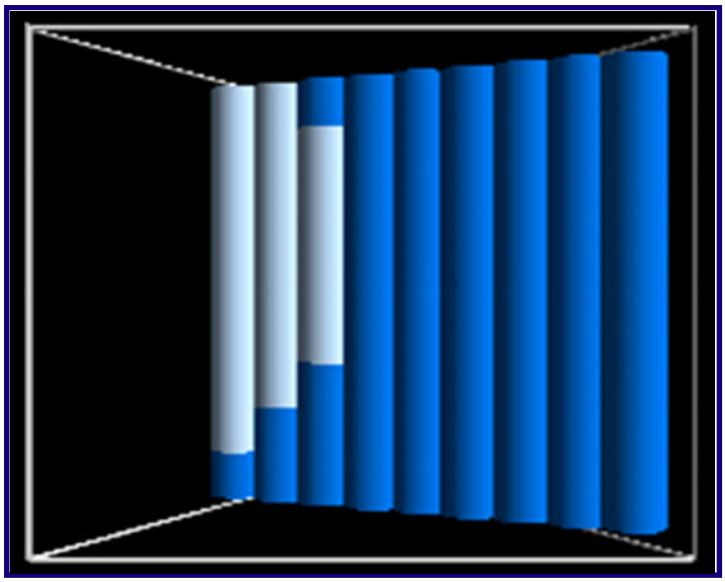

Figure 7: 3D representation of the equilibrium phase behaviour for {Miglyol 812/Imwitor 308} (4:6)-Tagat S2 with no drug resulting from the incremental addition of water.

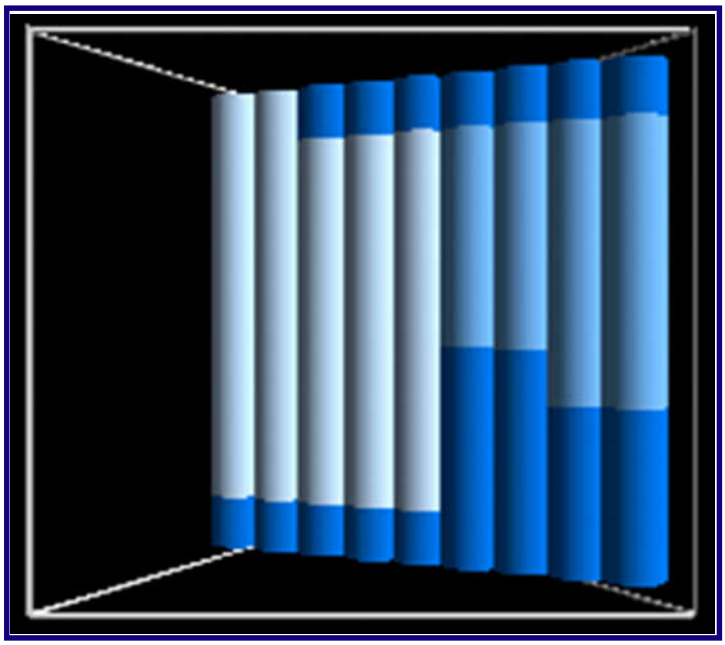

Figure 8: 3D representation of the equilibrium phase behaviour for {Miglyol 812/Imwitor 308} (4:6)-Tagat S2 with 10% ibuprofen resulting from the incremental addition of water.

on the phase behavior map during dilution with water. Furthermore, at least 70 % w/w of Cremophore RH40 is needed to cause L_1+L_2 phase to disappear from phase behavior map in comparison to using 50% w/w Tagat S2, see Figs 6 and 8. It is thought that the appearance of L_1+L_2intermediate turbid phase during emulsification process which takes place in the stomach might be detrimental to the bioavailability enhancement of poorly water soluble drugs. Nonetheless, the formation of LC clear lyotropicmesophases might form sustained release systems.

4. CONCLUSION

In order to design successful self-micro-emulsifying lipid systems, pre-formulation studies which affect the performance of resultant dispersions of these systems with and without drug should be carried using suitable emulsification media.It appears that drugs can interfere in the mechanistic processes of emulsification by blocking charge transfer during dispersion of the formulation.

5. ACKNOWLEDGMENT

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