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SELF-MICROEMULSIFYING TYPE II LIPID CLASS SYSTEM: INHIBITING SALTING OUT EFFECT OF ELECTROLYTES PRESENT IN THE EMULSIFYING MEDIA

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ABSTRACT

One important element in the formulation design of a successful oil based system is the ability of the lipid composite to retain its solvent capacity after dilution in the physiological media. There is a trend of moving towards extremely hydrophilic systems in order to improve the bioavailability of lipophilic compounds. This, however, raises concerns regarding the loss of solvent capacity after dispersion, hence inducing drug crystallization. In this investigation, self-microemulsifying systems composed of either hydrophilic or water insoluble components were developed. Various hydrophilic polymers were also screened for masking the salting out effect of electrolytes present in the emulsification media. Two lipid mixtures containing (a) Miglyol 812/Imwitor 988/ Cremophor EL (hydrophilic) or (b) Captex 300/Caprol PGE 860/Acconon CC-6 (lipophilic) were optimized for self-microemulsification; droplet size was measured using PCS. Lipid mixtures were emulsified in electrolyte solution (SGF) containing various polymers including; PVP, PEG 6000, Lutrol F68 or Lutrol F127. Phase diagrams showed self-microemulsifying mixtures with optimal blends of Miglyol 812/Imwitor at ratios of 5:5 using 30% w/w Cremophor EL, or Captex 300/Caprol PGE-860 at ratios 3:7 with Accnon CC 60% w/w. Electrolytes present in the media only affected the emulsification of the system with the water insoluble excipients. This effect was inhibited by including Lutrol F127. A potential self-microemulsifying system was developed using water insoluble materials. Solvent capacity of this system is unlikely to be compromised hence avoiding drug precipitation. Lutrol F127 was found to counteract the effect of electrolytes in the media.

Keywords: SMEDDS, SEDDS, Poloxamer 407, Oil formulations and Poorly water-soluble drugs

INTRODUCTION

There is an increasing interest in the field of lipid based technology as an approach to improve the bioavailability of poorly-water soluble compounds. It has been estimated that approximately 60–70% of the drug molecules are insufficiently soluble in aqueous media and/or have very low permeability **[1]**. Hence, there is rampant increase in the number of research work in this area **[2]**. These systems have a profound impact in the pharmaceutical industry, as the number of marketed products using this technology is growing. This includes; Neoral® (Cyclosporin A/I, Novartis), Gengraf® (Cyclosporin A/III, Abott), Accutane ® (Isotretinoin, Roche), Cipro® (Ciprofloxacin, Novartis), Agenerase® (Amprenavir, Glaxo SmithKline), Lipirex® (Fenofibrate, Sanofi-Aventis), Aptivus® (Tipranavite, Boehringer Ingelheim), Kaletra® (Lopinavir and Ritonavir, Abott), Lamprene® (Clofazamine, Alliance laboratories) and Sustiva® (Efavirenz, Bristol-Meyers) **[3-6]**. Self-emulsifying or self-micro-emulsifying drug delivery systems (SEDDS or SMEDDS) are considered types of lipid based technology. SEDDS or SMEDDS are isotropic mixtures of oils (triglycerides), and/ or co-surfactant (mixed glycerides) and non-ionic surfactants (HLB 12 to 17] which upon gentle agitation spontaneously emulsify in water producing fine oil in water (o/w) dispersions of droplets <5µm **[5]** or 5 to 140nm **[7-8]**, respectively. It is anticipated that SMEDDS due to dispersions of relatively small particle size with large surface area available for drug diffusion might have a profound impact on the bioavailability enhancement of lipophilic compounds **[9-11]**. This is evident in the reformulation of cyclosporine A as Neoral® **[11]** versus the earlier 'Sandimmune' formulation, which was a coarsely emulsifying system **[12]**. Depending on the polarity of the oil mixture, particle size of the resultant dispersion and the formulation digestibility, lipid systems were classified into five types; type I, II, IIIA, IIIB and IV **[13-14]**. Moving from type 1 into type 4 lipid class systems results in increasing hydrophilicity of lipid mixture as, more hydrophilic surfactants and/or co-solvents constituents are included in the lipid matrix. Type IV formulations do not contain any natural oils and hence represent the most hydrophilic formulations of all. Recently, formulation scientists start opting for Type IV class formulations as in the case of 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 **[15]**. Nonetheless, poorly-water soluble drugs formulated with type IV lipid class carriers are prone to crystallization in the lumen of gut after dispersion. These carriers tend to lose their solvent capacity during emulsification process as there is no enough nonpolar content in the lipid matrix to hold the drug in the amorphous form and thus circumvent drug precipitation. Type II lipid formulations are defined as self-emulsifying formulations that consist of water insoluble components; the drug is dissolved in triglycerides and/ or mixed glycerides blended with non-ionic surfactants of HLB between 10-12. Various studies **[9-10, 16-17]** have shown that electrolytes present in the emulsification media can affect the emulsification performance of type II lipid formulations as they contain surfactants with low HLB values (< 12) such as; Tween 85 or Tagat TO. Due to salting out effect the preferential aqueous solubility of the surfactant in this case is shifted to the oil phase inducing phase separation. A self-micro-emulsifying type II lipid system was developed using Miglyol 812/Imwitor 988/Tagat TO **[10]**. The importance of these robust self-micro-emulsifying systems lies behind the fact that they are composed of water insoluble materials and therefore tend not to loose their solvent capacity after emulsification event, minimizing drug precipitation in the gut. Nonetheless, recent studies have shown that the emulsification of oil system composed of Miglyol 812/Imwitor 988/Tagat TO in aqueous media containing electrolytes resulted in significant increase in the oil droplet size values in comparison to formulation dispersion in water alone **[10, 18-19]**. Furthermore, depending on ionic strength of emulsification media and the amount of Imwitor 988 which was included in the oil mix, these systems have shown propensity of phase separation due to salting out effect of electrolytes. This might compromise bioavailability of drugs included in these systems and therefore restrict their applications as vehicles for drug delivery.

In this investigation, self-microemulsifying systems composed of either hydrophilic or water insoluble components were developed. Various hydrophilic co-solvents including lutrol F68 (Poloxamer 188), lutrol F127 (Poloxamer 407), polyvinylpyrrolidone, labrasol and PEG 6000 were screened in an attempt to avert salting out effect of electrolytes present in the emulsification media.

MATERIALS AND METHODS

Materials

Miglyol 812 (medium chain triglyceride) and Imwitor 988 (C_8/C_{10} mono/diglycerides) were supplied by Condea Chemie GmbH. Captex 300 (Caprylic/capric triglyceride), Caprol PGE 860 (Polyglycerol-10 mono-dioleate) and Acconon cc-6 (Polyoxyethylene 6 Caprylic/Capric Glycerides) were supplied by Abitec Corporation. Cremophor EL (polyoxyethylene-(35)-caster oil), Lutrol F68 (Poloxamer 188), Lutrol F127 (Poloxamer 407), Kollidon (Polyvinylpyrrolidone) and Ibuprofen were obtained from BASF Corporation. Labrasol (Caprylocaproyl polyoxyl-8 glycerides) was obtained from Gattefosee. All water used was Mili Q water.

Methods

Self-emulsification

Excipients were accurately weighed into screw-capped glass vials with secure closures; in the following order: oil, co-surfactant, surfactant and then co-solvent. The top of each glass vial was rapped with cling film before being tightly closed. Each glass vial was then heated at around 50° C in a thermostated water bath for approximately 1 minute. After thorough vortexing, lipid mixtures were placed in the oven over night and allowed to equilibrate at 25° C. An amount of 1gm of each mixture was introduced into 100ml of either Mili Q water or simulated gastric fluid (SGF) without pepsin (see table below) in a 500 in a 500-ml glass beaker. Emulsification was carried out at 25° C or 37° C in a thermostatically controlled mechanical shaker set at 100 oscillation per min for 15 minutes. All materials were left equilibrate to the appropriate temperature prior carrying emulsification event.

Table 1: Components of simulated gastric fluid (SGF) without pepsin

NaCl	HCl	Water (qs)	pH
2 g	7 ml	1000 ml	1.2

Loading of drug

An amount of Ibuprofen was accurately weighed into glass vials containing self-micro-emulsifying lipid mix to obtain a final concentration of 100mg/g lipid. The top of each glass vial was then rapped with a cling film before screwing on the cap. Each vial was then sonicated for around 10 minutes to facilitate the dissolution of ibuprofen in the lipid formulation, followed by a thorough vortexing.

Thermal infusion of solid co-Solvents

Solid co-solvent systems such Lutrol 68 or 127 was weighed into glass vials containing lipid mixtures with dissolved drug to obtain concentrations of 20% or 40 % of polymer in the oil pre-concentrate. Formulation were then placed in a thermostated water bath and

heated at around 80° C until full melting, followed by a thorough vortexing. Formulations were then sonicated for few seconds and left to solidify at room temperature.

Particle size analysis

The mean emulsion droplet diameter (MEDD) for lipid formulation with and without drug after aqueous dispersion was measured using Quasi-elastic light scattering (QELS, Malvern model LO-C photon correlation spectrometer). Experiments were performed in triplicate. Size distributions of the resultant emulsions were obtained and expressed as mean values of all data ± standard error.

RESULTS AND DISCUSSION

Self-emulsification of type ii and type iii lipid class systems

Type II lipid class systems are defined as self-emulsifying formulations that consist of water insoluble components. Source of triglyceride (oil) or mixed glycerides are blended with nonionic ester ethoxylate surfactants with HLB values between 10-12, such as; polysorbate 85 (Tween 85) or polyoxyethylene 25-glyceryl trioleate (Tagat TO) to promote emulsification. This type of formulation is likely to retain its solvent capacity for the drug after dispersion in aqueous media [9, 19-20]. Depending on the surfactant concentration, type II systems produce self-emulsifying formulations of droplet size diameters of approximately 250 nm as in the case of blends of Miglyol 812 (medium chain triglyceride (MCT)) and Tagat TO (non-ionic surfacatant) **[17]**. Nonetheless, a robust self-microemulsifying formulation of particle size with droplet diameters of ~50 nm was developed by by incorporating medium-chain glyerides, particularly C_8/C_{10} mono/diglycerides such as Imwitor 988 which acts as a co-surfactant as in the blends of {Miglyol 812/Imwitor 988} and Tagat TO .

Figures 1 & 2 below depict self-microemulsifying regions of resultant dispersions of the various blends of Captex 300 (MCT), Caprol PGE 860 (co-surfactant) and Acconon cc-6 (non-ionic surfactant, HLB value = 12) emulsified at 25°C and 37°C, respectively. Oil mixtures of Captex 300/Caprol PGE 860/Acconon cc-6 are classified as type II lipid class system as they are composed of water insoluble materials. Hence, very restricted self-microemulsifying region of clear dispersions demarked by the blue triangles is obtained at room temperature, see **Figure 1**. Optimum self-micro emulsification at 25°C was obtained for {Captex 300/Caprol PGE 860}/Acconon cc-6 lipid mixture at ratios of 40{3/7}/60

Nonetheless, area of self-microemulsifying systems was further suppressed on emulsification at 37°C, as only few oil mixtures formed clear aqueous dispersions, see **Figure 2**. Generally, variations in emulsification temperature and electrolytes present in the emulsification media can affect the emulsification performance of lipid formulations. At elevated temperatures, non-ionic surfactants often become increasingly more lipophilic. Increase in temperature can decrease hydration of the surfactant and thus ensues change in micellar shape, size and eventual loss of aqueous solubility. This is analogous to reducing the HLB of the surfactant. The change in nonionic surfactant-oil-water system (nSOW) phase behaviour with temperature can result in the phase transitions Winsor's type I (o/w emulsion) to type II (w/o emulsion), see **Figure 3**. The emulsification at temperatures higher than phase inversion temperature (PIT) of the emulsifier is generally accompanied by corresponding increase in the emulsion droplets. Hence, self-microemulsifying region is further receded at elevated temperature. This pattern is clearly proved in the effect of the emulsification temperature on the mean volume diameter of o/w-type emulsions of Miglyol 812-Tagat TO system with or without Imwitor 988 studied by Hasan *et al* **[10]**.

A sharp increase of almost 2 folds in the mean emulsion diameter occurred at emulsification temperatures above 40ºC for the system containing 85% Miglyol 812 and 15% Tagat TO **[9]**. This suggests that phase inversion to w/o-type emulsion due the loss of the surfactant's affinity for the aqueous phase has occurred which resulted in larger emulsion droplets. Nonetheless, when the system contained 3-4 or 5 parts of Imwitor 988, optimum temperature for emulsification occurred at 20ºC or 30 º C, respectively. According to a recent study by Hasan *et al* **[10]**, Imwitor 988 as a polar oil causes depressions in PIT which means that emulsion type inversion from o/w to o/w occurs at lower temperatures causing growth in oil droplet size. This action, however is a concentration dependent and moreover, is highly likely to be averted by using surfactants with relatively high HLB values (>12).

Furthermore, type III systems are also called self-microemulsifying systems, as optical clarity can be achieved with these formulations, very fine dispersions (50-100nm) can be produced under conditions of gentle agitation. These systems besides triglycerides and/ or mixed glycerides

contain hydrophilic components including hydrophilic nonionic surfactants (HLB > 12) such as, Cremophor RH40, Cremophor EL, Emuline or Tween 80, and or hydrophilic co-solvents such as, Ethanol, Propylene glycol or Polyethylene glycol. An archetypal example of a Type III system is the reformulation of cyclosporine A as Neoral® **[11]**.

Figure 4 depicts self-microemulsifying region for a type III lipid composed of Miglyol 812 (MCT), Imwitor 988 (co-surfactant) and Cremophor EL (non-ionic surfactant). An extended area of self-microemulsifying region, as demarked by blue triangles, is observed **(Figure 3)** vis-à-vis limited area of self-microemulsification in the case of Captex 300 (MCT), Caprol PGE 860 (co-surfactant) and Acconon cc-6, see **Figure 1**. Optimum micro-emulsification was obtained at Miglyol 812/Imwitor 988 ratios of (3:7) line (ab), (4:7) line (ac), (5:5) line (ad) or (6:4) line (ae) using Cremophor EL at concentrations ≥ 20% w/w. This reflects the hydrophilic nature of the Miglyol 812:Imwitor 988:Cremophor EL lipid mixture manifested by the ability of Cremophor EL in solubilising large quantities of oil and thus forming O/W micro-emulsion. Cremophor EL (polyoxyethylene-(35)-caster oil) is the liquid form of Cremophor RH 40 (polyoxyethylene-(40)-hydrogenated caster oil). Cremophor RH 40 has a high melting point of ≈ 40ºC and hence is a waxy material at room temperature. This poses problems in scale-up production of lipid molten formulations on automated equipment. Solidification of the lipid system and thus drug precipitation can occur during processing. Comparable self-emulsification profiles from oil blendes containing either Cremophor EL or RH40 were obtained in a recent study by Hasan *et al* **[18]**. This shows that Cremophor EL as a liquid form can be used in fabricating lipid formulation without crystallization due to variations in environmental temperatures and hence, can be a good and practical alternative to using RH40 in lipid based products. Cremophor RH40 was firstly used in Neoral® to replace the earlier 'Sandimmune' formulation, which was a coarsely emulsifying system **[12]**. Since then, Cremophor EL or RH40 has been widely used to in the production of many lipid formulation products including; Kaletra® and Norvir® (Abbott), Aptivus (Boehringer Ingelheim) and Infree (Eisai Co.) **[21-22]**. In another study, extended areas of self-microemulsifying systems were obtained using (Miglyol 812/Imwitor 308)$_{oil}$ and Tagat S2 (PEG-(20)-glyceryl stearate) or Tagat S

(PEG-(30)-glyceryl) as hydrophilic surfactants with HLB values of 15 or 16.4, respectively **[23]**. The study concluded that, emulsification performance of lipid composites containing Cremophor RH40 is relatively better than using Tagat S2 or Tagat S in the oil mix. This was attributed to the variations in the HLB values and packing parameters of these non-ionic surfactants. Flexible bilayer aggregates are possible formed in the case of Cremophor RH40 while for Tagat S or S2 spherical or cylindrical aggregates are favoured.

Effect of electrolytes on the emulsification of lipid systems

Electrolytes present in the dispersion media have similar effect to temperature on the emulsification performance of lipid formulations. Both electrolytes and temperature reduce affinity of surfactants towards aqueous interface by decreasing their hydrophilicity and thus ultimately induce phase separation. The effect of electrolytes on the emulsification behaviour of this system without drug was thoroughly studied in by Hasan *et al*. **[19]**. Generally, ionic strength or electrolytes in the emulsification media can cause dehydration in the hydrophilic core as if hydrophilic moiety is being constantly severed. As a result, hydrophilicity of the non-ionic surfactants is reduced and thus surfactants become more soluble in the oil phase and eventually phase separation occurs. This effect will depend on the inclusion of high polar oil in the formulation like Imwitor 988 and moreover, the use of non-ionic surfactant with relatively low HLB (< 12) such as, Tagat TO or Acconon cc-6. In this case, the reduction in the HLB of the surfactant incurred by the presence of electrolytes in the emulsification media will be sufficient to cause shift in its solubility from the aqueous to the oil phase which results in phase separation and eventually crystallization of the dissolved drug. This was evident in the case of a self-micro-emulsifying system representing type II lipid class system composed of Miglyol 812/Imwitor 988/Tagat To **[19]** or an oil system containing Captex 300/Caprol PGE 860}/Acconon cc-6 lipid mixture at ratios of 40{30/70}/60. The emulsification of a system composed of Miglyol 812/Imwitor 988-Tagat TO {70(60/40)30}system containing a lipophilic model drug in media containing electrolytes which represents fasted state conditions in the small intestine has ensued in complete phase separation **[19]**. Nonetheless, the emulsification of the aforementioned system in media containing electrolytes plus

endogenous amphiphilic biliary components including lecithin and bile salts has maintained homogenized o/w dispersion. Yet, increases in oil droplet size were observed in these dispersions in comparison to the emulsification in pure water. It is highly likely that electrolytes present in the GIT due salting out effect will compromise bioavailability of lipid systems containing surfactants with relatively low HLB. Such systems have to rely on digestion by lipolysis cascade that takes place mainly in the small intestine to free the drug. Yet, the tendency in the growth of oil droplet size of those systems due to ionic strength of solutions might minimize propensity of drug crystallization during its passage in the GIT. In this case, the drug is sequestered in the oil droplets with minimal contact with the surrounding aqueous media and thus drug precipitation is circumvented. Yet, for more hydrophilic type 1V lipid class system the drug is highly exposed to the aqueous environment and thus prone to precipitation. The effect of the ionic strength of the emulsification media was also observed in the system which is composed of Miglyol 912/Imwitor 988/Tagat S2 **[23]**.

The effect of ionic strength of the emulsification media on the dispersion of various lipid formulations with varying degree of hydrophilicity is summarized in the systematic representation depicted in **Figure 5**. The emulsification of SMEDDS oil systems which contain low HLB surfactants such as Tagat TO or Tween 85 in the presence of electrolytes will cause dehydration of the surfactants polar moieties. This will reduce HLB values of surfactants rendering them more soluble in the oil phase which ultimately ensue in phase separation, **Figure 5**, path (a). On the other hand, in the case of oil systems containing surfactants with high HLB values such Cremophor RH40 or Tween 80 any reduction in the HLB value of surfactants due to ionic strength of emulsification media will not be enough to cause phase separation, as in path (b) **Figure 5**.

Effect of co-solvents on the emulsification of lipid systems

Generally, co-solvents are used in the oil mix to aid in solubilizing the drug to achieve required dose and to increase the solubility of surfactants in the oil phase. Co-solvents which are used to prepare lipid formulations include; propylene glycol, poly-ethylene glycol 400, ethyl alcohol, transcutol, poloxamers and glycofurol. There is no evidence that co-solvents can interfere in the mechanistics of emulsification aftermath event of aqueous dispersion unless co-solvent

has surface activity. However, there is trend amongst research scientists to opt for hydrophilic systems such as type IV lipid class system as in Agenerase® (amprenavir) or co-solvent based system as in Nurofen® (Ibuprofen). It is anticipated that these lipid carriers form clear microemulsion on dilution with water all the way through from 0 -100 % w/w. After the gradual penetration of water during emulsification process there are no intermediate phases forming that would compromise bioavailability. Yet, these systems are at risk of drug precipitation after dispersion, as hydrophilic components diffuse out to the aqueous medium leaving the drug which they have carried within its matrix to crystallize. In vitro studies have shown that the amount of non-polar components is crucial to circumvent drug precipitation and moreover, including only 10-20% PEG in the lipid mixture accelerates crystallization of drug **[19]**. Nonetheless, although in vitro studies have substantiated that extremely hydrophilic systems such as Agenerase® or Nurofen® might be prone to drug crystallization, these products still work in vivo with good bioavailability profiles. This apparent in vivo-in vitro paradox reflects the complexity of digested food content and the limited available amount of aqueous medium in the gastrointestinal tract to causing drug precipitation.

Figure 6 shows the effect of lutrol F127 on the mean emulsion droplet size (MEDD) of aqueous dispersions of lipid system composed of {Captex 300/Caprol PGE 860}/Acconon cc-6 lipid mixture at ratios of 40{3/7}/60 with and without drug. The emulsification of the lipid system which is composed of Captex 300/Caprol PGE 860}/Acconon cc-6 without added polymer or drug has produced clear micro-emulsion of particles of ≈ 90 nm. This system is classified as type II lipid class system which is composed of water in-soluble materials. The inclusion of ibuprofen at 100 mg/g in the lipid mix without polymer (lutrol F127) has sharply increased particle size of the resultant dispersion of almost 4 folds. It is thought that the inclusion of a model drug interferes in the mechanistics of emulsification either by complexing with certain excipients in the lipid mixture by interacting with the liquid crystalline phase **[24-25]**. Similar findings were observed using various drugs such as flurbiprofen **[26]**. On the other hand, the progressive inclusion of lutrol F127 in the lipid mix without drug has not influenced particle size of the resultant dispersion until including polymer at concentration of 40% w/w in the lipid matrix. In this case, mean

emulsion droplet size of dispersion was reduced by half in comparison to emulsification of pure oil mixture without polymer. Nonetheless, obvious corresponding reductions in the oil droplet size were observed on progressive inclusion of lutrol F127 in the lipid mix containing drug. Almost 2 or 10 folds decrease in the droplet size occurred when lutrol F127 was included respectively at concentrations of either 20 % or 40 % w/w in the oil mix containing drug. Almost clear dispersions were obtained when including lutrol F127 at concentrations of 40% w/w in the lipid mixture containing ibuprofen at 100 mg/g. This reflects the high solubilization capacity of lutrol F127 towards oil mix and model drug in the aqueous media.

In an attempt to avert salting out effect of electrolytes present in the emulsification media in the case of self-micro-emulsifying class II lipid class system. This includes; Miglyol 812/Imwitor 988/Tagat TO or Captex 300/Caprol PGE 860/Acconon cc-6 lipid systems. Various co-solvent systems including lutrol F 68 (Poloxamer 188), lutrol F127 (Poloxamer 407), polyvinylpyrrolidone, labrasol and PEG 6000 were included in the lipid vehicle to investigate their possible role in masking the effect of electrolytes present in the emulsification media. Only lutrol F127 (see **Figure 7** for chemical structure) was able to circumvent salting out effect due to ionic strength of emulsification media. As the picture presented in **Figure 8** shows, emulsification of lipid vehicle which is composed of {Captex 300/Caprol PGE 860}/Acconon cc-6 at ratios of 40{30/70}/60 in SGF media has ensued in complete phase separation in comparison to clear dispersion in distilled water. This reflects the role of electrolytes in dehydrating polar moieties of non-ionic surfactant rendering them less soluble in water by reducing their HLB values and hence inducing phase separation. Nonetheless, the inclusion of lutrol F127 in the lipid vehicle at concentration of either 20 or 40% w/w in the lipid mixture has masked salting out effect of electrolytes. Clear dispersions were obtained after emulsification of lipid vehicle containing lutrol in SGF.

The systematic representation of the role of lutrol F127 in masking the salting out effect of electrolytes present in the emulsification media is depicted in **Figure 9**. Salt ions compete with polar moieties of surfactant and co-surfactant for water molecules. Therefore, water molecules at the oil water inter phase are attracted by salt ions. This will cause dehydration in the hydrophilic moieties of the oil mix and thus increasing

non-polar interactions within oil droplets and ultimately induces phase separation, see **Figure 9**, path (a). Nonetheless, when lutrol F127 is included in the oil mix, after dispersion of formulation in media containing electrolytes, lutrol F127, due to its affinity to the oil phase, encapsulates oil droplets, see **Figure 9** path (b). This, from one hand, raises HLB value of oil droplets and thus any reduction in the HLB value incurred by electrolytes will be counteracted. From the other hand, lutrol F127-oil complex acts as a shield preventing direct contact with electrolytes ions and thus preventing salt out effect and system phase separation.

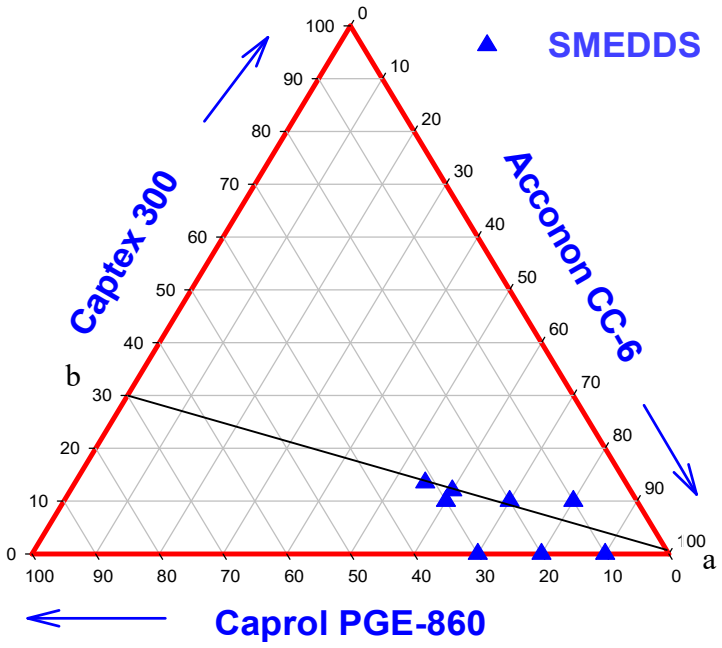

Figure 1: Self-microemulsifying regions of resultant dispersions of the various blends of Captex 300 (MCT), Caprol PGE 860 (co-surfactant) and Acconon cc-6 (non-ionic surfactant, HLB value = 12) emulsified at 25°C. Blue triangles (▲) represent self microemulsifying region of clear dispersions

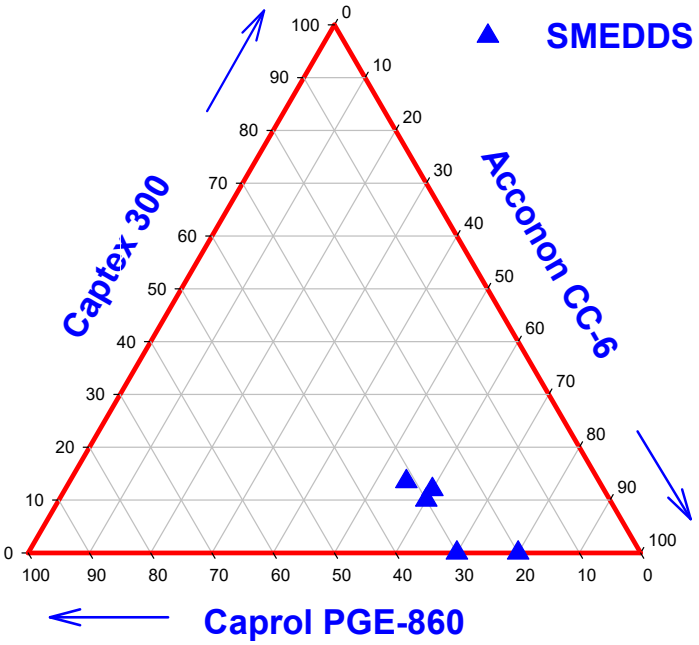

Figure 2: Self-microemulsifying regions of resultant dispersions of the various blends of Captex 300 (MCT), Caprol PGE 860 (co-surfactant) and Acconon cc-6 (non-ionic surfactant, HLB value = 12) emulsified at 37°C. Blue triangles (▲) represent self microemulsifying region of clear dispersions

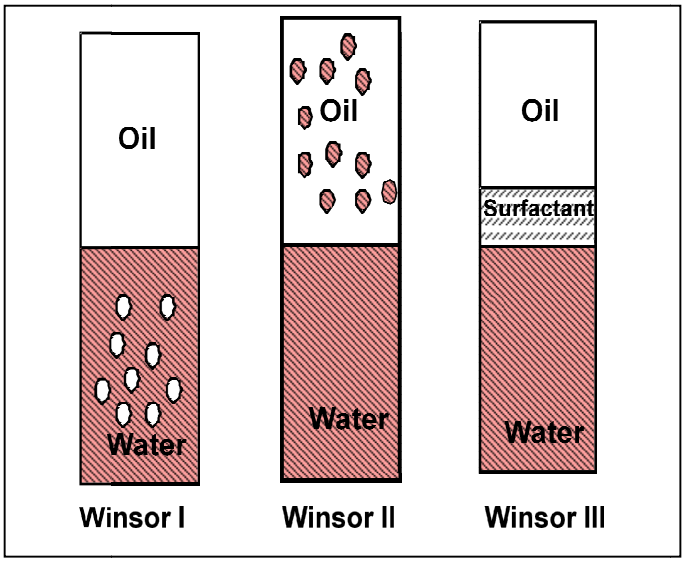

Figure 3: Winsor's description of various types of emulsion systems

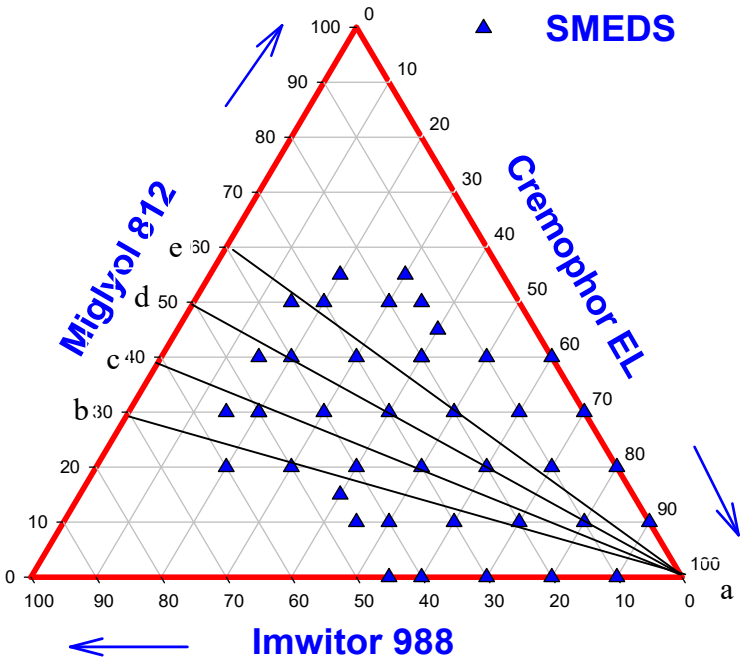

Figure 4: Self-microemulsifying region for type III lipid composed of Miglyol 812 (MCT), Imwitor 988 (co-surfactant) and Cremophor EL (non-ionic surfactant) emulsified at 25°C. Blue triangles (▲) represent self microemulsifying region of clear dispersions

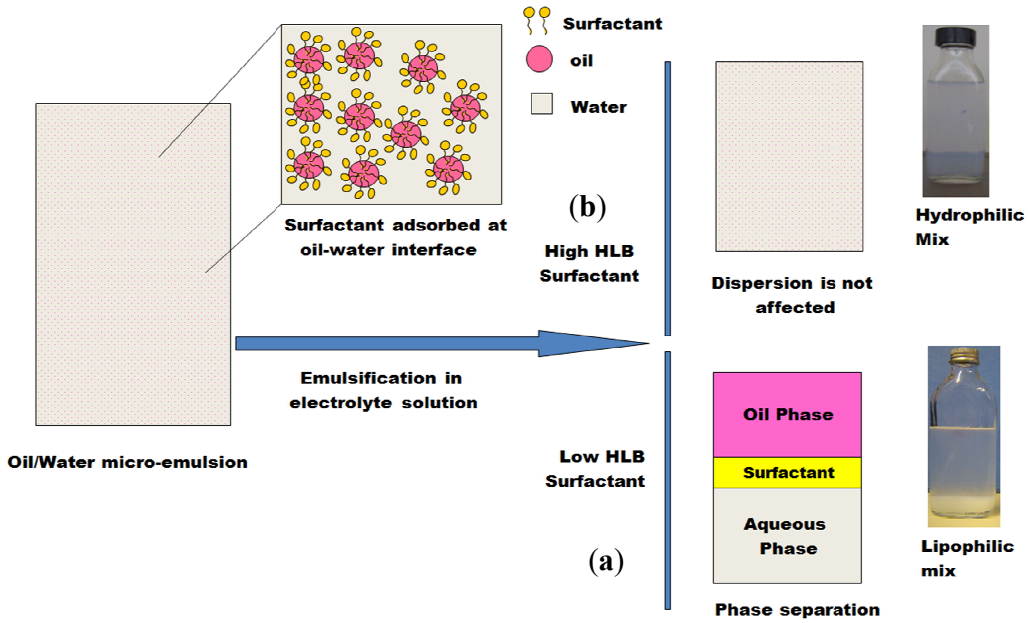

Figure 5: Systematic representation of the effect of ionic strength of emulsification media on the dispersion of various lipid formulations with varying degree of hydrophilicity

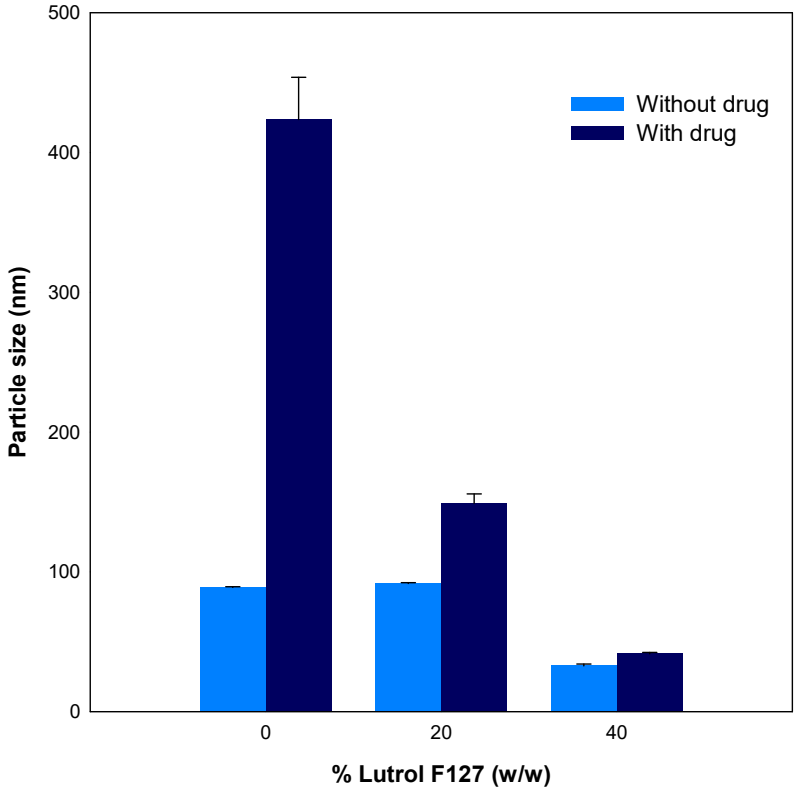

Figure 6: Effect of lutrol F127 on the mean emulsion droplet size (MEDD) of aqueous dispersions of lipid system composed of {Captex 300/Caprol PGE 860}/Acconon cc-6 lipid mixture at ratios of 40{3/7}/60 with and without drug

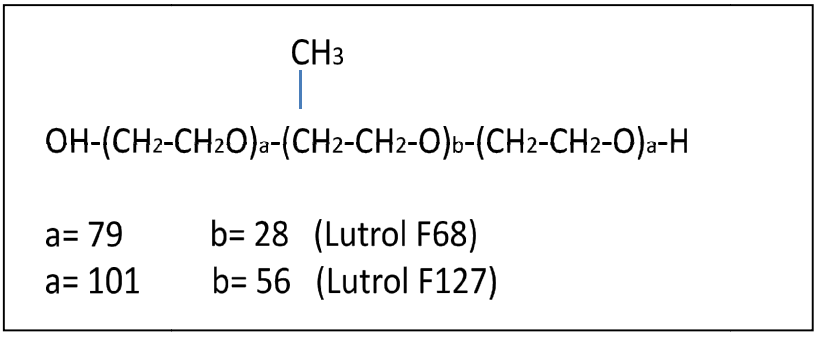

Figure 7: Chemical structure of Lutrol F68 and F127

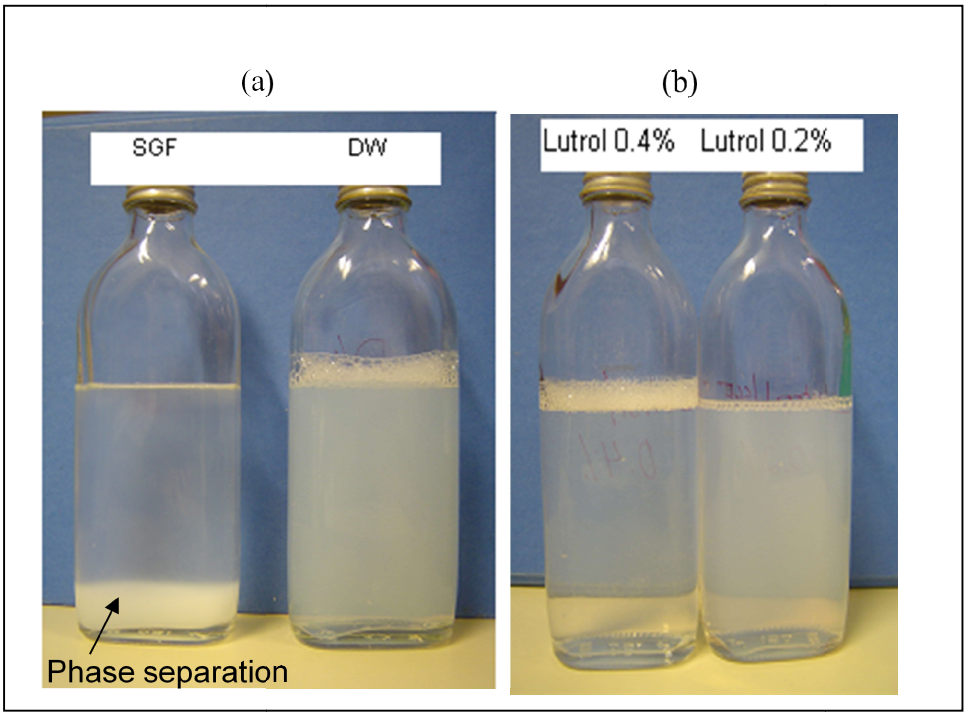

Figure 8: Pictures showing (a) Salting out effect of electrolytes present in the emulsification after dispersion of lipid vehicle which is composed of {Captex 300/Caprol PGE 860}/Acconon cc-6 at ratios of 40{30/70}/60 in SGF media. (b) Effect of lutrol F127 on averting phase separation due ionic strength of media after emulsification in SGF

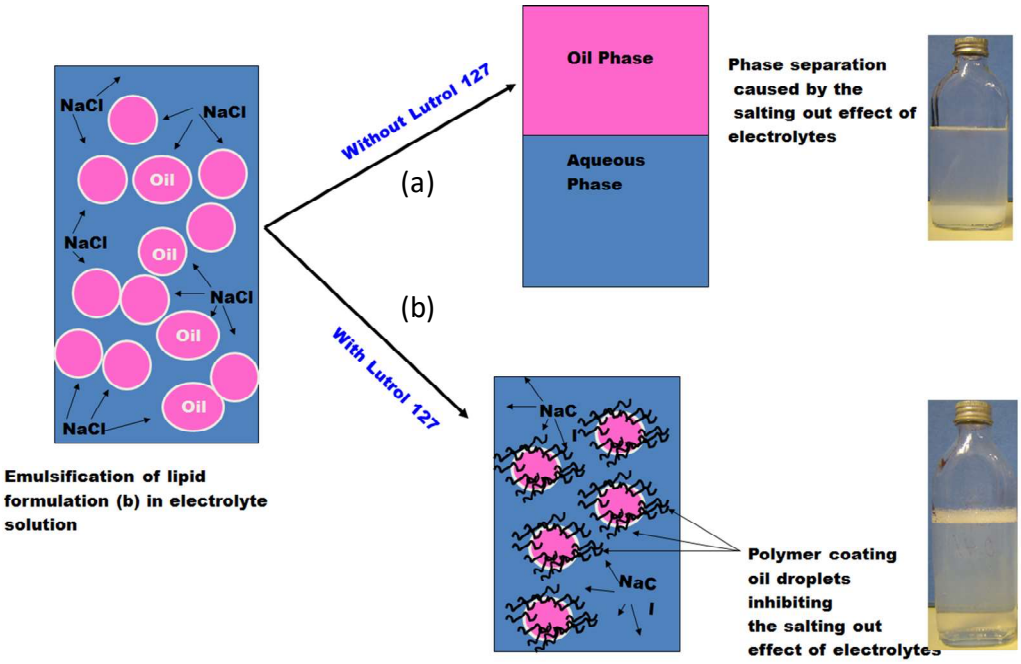

Figure 9: Systematic representation of the role of lutrol F127 in masking the salting out effect of electrolytes present in the emulsification media

CONCLUSION

Robust self-micro emulsify type II lipid class system which is composed of {Captex 300/Caprol PGE 860}/Acconon cc-6 at ratios of 40{3/7}/60 was developed. The importance of this system is due to the fact that it is composed of water insoluble materials which tends not to loose its solvent capacity after dispersion minimizing precipitation of drug in the gut. Nonetheless, this system was prone to the salting out effect of electrolytes present in the media which might compromise it's in vivo application. However, lutrol 127 was found to inhibit salting out effect of electrolytes by acting as a shield preventing direct contact with electrolytes.

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Conflicts of Interests

Author has none to declare

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