Development of potential Self-microemulsifying lipid formulation for the oral administration of Curcumin

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ABSTRACT

Objective: The objective of the present study was to design and develop stable o/w micro-emulsions for the oral delivery of Curcumin. The empirical role of medium-chain triglyceride (MCT) or long-chain triglyceride (LCT) on the emulsification mechanistics of SMEDDS was studied. The effect of type of vehicle on the fate of drug after dispersion was also investigated.

Methods: Miscibility profiles and self-micro-emulsifying regions for various lipid systems were screened by varying types of oil, cosurfactant and surfactant. Solubility of Curcumin was measured in various optimized vehicles.Dynamic equilibrium phase studies were performed and phase boundaries were determined for the lipid-water systems.

Results: An archetypical Type IIIA micro-emulsion system comprising 21%w/w Crodamol GTCC, 49%w/w Glycerox 767HC and 30% w/w Etocas 35 HV was developed which can potentially mimic the bioavailability of Curcumin. MCT or LCT included in SMEDDS appears to influence emulsification process by either increasing or decreasing number of transient stages before obtaining o/w microemulsion.

Conclusion: Potentialself-micro-emulsifying lipid formulations representing Type IIIA systems were developed for the oral administration of lipophilic drugs. Nonpolar components in the lipid matrix appear to be crucial in maintaining solvent capacity on dispersion and hence prevent crystallization of drug.

Key Words SMEDDS; Lipid formulations; Curcumin and poorly water-soluble compounds

INTRODUCTION

Self-emulsifying drug delivery systems (SEDDS) are considered one of the promising approaches to overcome the formulation difficulties of various lipophilic drugs and hence to improve the oral bioavailability of poorly absorbed drugs. SEDDS are isotropic mixtures of oils (triglycerides), and/ or co-surfactant (mixed glycerides) and non-ionic surfactants which spontaneously emulsify in water upon gentle agitation producing fine oil in water (o/w) dispersionsof droplets <5µm[1]. On the other hand, the inclusion of hydrophilic components including hydrophilic surfactants (HLB >12) and/ or hydrophilic co-solvents in the lipid mix can produce systemswhich emulsifies spontaneously when mixed with water under gentle agitation forming an almost clear o/w microemulsion of droplets with diameters between 5 and 140nm[2]. These systems are identified as Self-micro-emulsifying drug delivery systems

(SMEDDS). The difference between a microemulsion (SMEDDS) and an emulsion (SEDDS) is shown below in the photograph in figure 1.

Both SEDDS and SMEDDS can reduce the inherent limitation of slow and incomplete dissolution of poorly- water soluble drugs, and facilitate the formation of solubilised phases from which absorption may occur[3]. Therefore, one advantage that self-emulsifying formulations have over solid dosage formulations is the avoidance of slow drug dissolution. Such lipid formulations will present a lipophilic drug in oily solution with a large interfacial area across which diffusion can take place. The mechanisms, rate and extent of drug absorption from the resulting emulsion will be strongly dependent on the oils and surfactants used in each formulation. In addition, distribution of the emulsion within the GIT may help to avoid the irritancy which can be caused

by contact between bulk solids and the gut wall.In order to facilitate the prospect of formulation design using lipid based technology, lipid systems were classified by Pouton[4]and updated in 2006[5]. Based on various physicochemical factors including, hydrophilicity of the oil mixture, particle size of the resultant dispersion and the formulation digestibility, Pouton[4,5] classified these systems into type I, II, III and IV as shown in table 1. These types result from blending up to five classes of excipients; ranging from pure triglycerides oils, mixed glycerides, lipophilic surfactants, hydrophilic surfactants and water soluble co-solvents. Table 1 describes the typical properties of the different types of lipid formulations. An archetypal example of a Type III system is the reformulation of cyclosporine A as Neoral[®6]. The drug was more available from the Neoral than the earlier 'Sandimmune' formulation, which was a coarsely emulsifying system[7].This might be due to the fact that the coarse emulsion produced by the Sandimmune formulation could not be reduced to colloidal dimensions because of limited digestion[4]. 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[8].

In this investigation, curcumin extracted from turmeric roots (Curcuma long L., Zingaberaceae) was selected as model lipophilic drug. Curcumin is the main coloring substance in Curcuma long and with other two related compounds; demethoxycurcumin and bisdemethoxycurcumin are known as curcuminoids, see figure 2 for chemical structures. Curcumin is currently undergoing clinical trials for several diseases including pancreatic cancer, familial adenomatous polyposis, atherosclerosis, inflammatory bowel disease, ulcerative colitis, neurological diseases, hypercholesterolemia, pancreatitis, psoriasis, chronic anterior, arthritis, Crohn's disease, uveitis and colon cancer[9]. Nonetheless, developing a pharmaceutical dosage form of curcumin poses many challenges for the formulation scientist due to its poor aqueous solubility, chemical instability in alkaline medium[10] rapid metabolism[11]and poor membrane permeation[12] which, all contribute towards the poor oral bioavailability of curcumin.The objective of the current study is to screen various lipid mixtures comprising oils, co-surfactants and non ionic surfactants in order to develop potential stable o/w micro-emulsions for the oral delivery of curcumin. Furthermore, the effect of lipid formulations representing type III and co-solvent based systems containing curcumin as a lipophilic model drug is also studied in an attempt to highlight the fate of the drug after dispersion in order to circumvent drug precipitation in the GIT.

MATERIALS AND METHODS
Materials
Crodamol GTCC (medium chain triglyceride), Crodamol PC (propylene glycol dicaprylate / caprate), Glycerox 767HC (PEG 6 caprylic/ capric glycerides), Croduret 50ss (PEG 40-45 Hydrogenated Castor Oil), Croduret 40ss (PEG 40 Hydrogenated Castor Oil) and Etocas 35 HV (PEG 35 Castor Oil) were all supplied by Croda as gift samples. Turmeric (*Curcuma longa*)was obtained locally in ground powder form. PEG 400 and Olive oil were supplied by Himedia, India. Oleic acid (USP) PRS-Codex purchased from Panreac, Spain. Ethanol absolute and n-Hexane 96%, analytical grade, ACS, USP were obtained from Scharlau, Spain.

Methods
Miscibility profiles for lipid mixtures
Regions of mutual solubility of various lipid formulations with wide range of surfactants that represent different HLB values were determined using ternary phase diagrams. Miscibility diagrams of various oils (Cordamol GTCC, Olive oil and oleic acid), co-surfactants (Glycerox 767HC, Crodamol PC) and surfactants including; Crodurate 60 ss, Crodurate 40 ss and Etocas 35 HV were constructed. Formulations of two grams which represent various percentages of oils, co-surfactants and surfactants on the ternary phase diagrams were weighed in 20 ml glass test tubes and then tops were wrapped with cling film. Mixtures were placed in a water bath at 50 ºC for 2 minutes before lipid components were thoroughly vortexed. Mixtures were then kept for 24-48 hours in an oven set up at 25°C before visual assessment. Mixtures which formed a continuous single phase were classified as miscible formulations. Samples that displayed two or more phases were described as immiscible systems.

Self-Emulsification profiles of lipid mixtures
Mixtures of the various oils, co-surfactants and surfactants were produced by accurately weighing ingredients into glass test tubes and then wrapped by cling 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 to equilibrate over night in an oven set up at 25°C. Emulsions were prepared under conditions of gentle agitation at a controlled temperature of 37°C. An amount of 1g of each lipid mixture was introduced into 100ml of distilled water in a 500-ml glass beaker held at 37°C in a thermostated water bath.

Emulsification under agitation conditions considered to be a reasonable simulation of the *in vivo* situation was carried out. Agitation was provided by gentle shaking on a mechanical shaker at 100 oscillations per min for 15 minutes. Visual assessment of resulting dispersions was carried out and systems which produced clear micro-emulsions were identified as SMEDDS.

Phase behaviour Study
Selected formulations were blended according to table 2. An amount of 4 g mixtures are made up by weight in screw-capped test tubes. Phase composition changes were made by adding water sequentially at 10 % w/w intervals. Mixtures were vortexed until homogeneity is achieved and then allowed to stabilize for phase identification.

Extraction of curcumin (curcuminoids)
Extraction of Curcumin was performed according to the method described by Popuri and Pagala[13] with slight modification. Turmeric; Curcuma longa Zingiberaceae, was obtained in a powder form. An amount of 100g of Turmeric powder was added to ethanol at ratio of 1:8 and stirred for approximately 24 hours. Suspension mixture of Turmeric and Solvent was filtered and the supernatant was collected. The filtrate which constitutes solvent and solute was loaded into a round bottom flask; using rotary evaporator under vacuum ethanol was partially removed. The formed slurry was then washed with stirring 3-4 times with hexane to cure curcumin and to dissolve any oleoresin or volatile oils. The formed solid aggregates of curcumin was then separated and left over night at ambient temperature to dry off solvent. Curcumin aggregates were pulverised into fine powder particles using mortar and pestle.

Calibration curve of curcumin
Calibration curve was constructed according the method described by Sharma et al.,[14]. An amount of 0.1g of extracted Curcumin was dissolved in 100 ml ethanol. Series of dilutions were made to obtain Curcumin concentrations ranging from 1µg to 7µg. Absorbance of the various solutions were measured by UV spectrophotometry at max 421nm.

Solubility of curcumin in lipid mixture
Curcumin is added in excess to either lipid formulation or co-solvent systems. Lipid suspensions are then vortexed for 3 minutes and then stored for 72 hours in a controlled temperature oven at 25°C to reach equilibrium (samples were vortexed in between). Oil suspensions are centrifuged at maximum speed (5300 rpm) for 15 minutes. The clear saturated oil solution is then removed and assayed analytically by UV spectrophotometry at max 421nm using a method described and validated by Sharma et al.,[14].

Self-emulsification of oil systems containing dissolved curcumin
A range of formulations representing type III or a co-solvent based system were prepared to probe the effect of including water-soluble surfactants or cosolvents on the fate of drug after dispersion. An amount of 1g of each formulation containing approximately 80mg curcumin was allowed to emulsify in 100 ml of water. Dispersions were then centrifuged at maximum speed (5300 rpm) for 15 minutes to monitor precipitation of drug.

RESULTS
Emulsification profiles of lipid formulations
Lipid systems containing medium-chain (C_8-C_{10}) triglyceride
Figure 3 shows the emulsification profile of a lipid system composed of Crodamol GTCC(oil), Glycerox 767HC (co-surfactant) and Croduret 50 ss (non-ionic surfactant). An amount of 1g of representative single-phase lipid mixtures was emulsified in 100ml, emulsions which produced optical clear dispersions were identified as SMEDDS. The ternary plot in figure 3 depicts a very limited area of SMEDDS.Figure 4 shows the emulsification profile of a lipid system composed of Crodamol GTCC(oil), Glycerox 767HC (co-surfactant) and Croduret 40 ss (non-ionic surfactant). Replacing Croduret 50 ss in the lipid mix (figure 3) with Crodurat 40 ss has significantly extended SMEDDS area as figure 4 illustrates.
Figure 5 shows the emulsification profile of a lipid system composed of Crodamol GTCC(oil), Glycerox 767HC (co-surfactant) and Etocas 35 HV (non-ionic surfactant). The ternary plot which depicts emulsification profile of the lipid composite of Crodamol GTCCGlycerox 767HC and Etocas 35HV (figure 5) has revealed an extended region of SMEDDS almost comparable to the lipid system containing Croduret 40 ss as a non-ionic surfactant (figure 4).

Lipid systems containing long-fatty acid chain (C_{16}-C_{18})
The ternary plot depicted in figure 6 shows SMEDDS region for a lipid system composed of Olive oil (long chain triglycerides; LCT), Crodamol PC (co-surfactant) and Etocas 35 HV. The emulsification profile of this system (figure 6) has revealed a very limited area of SMEDDS in comparison to lipid systems containing CrodamolGTCC (medium chain triglycerides; MCT), see figures 4 and 5.Figure 7

depicts self-micro-emulsifying profile for lipid composite of oleic acid, Crodamol PC and Etocas 35 HV. Substituting olive oil (figure 6) with oleic acid (figure 7) in the lipid mix though enhanced oil miscibility yet almost produced comparable SMEDDS regions.

Effect of type of oil on the phase behavior of lipid mix

Figure 8 displays the dynamic equilibrium phase behavior for various lipid systems with and without MCTs or LCTs on sequential dilution with water. In figure 8, aqueous-based liquids i.e. o/w micro-emulsions are denoted (L_1), oil-based liquids i.e. w/o micro-emulsions (L_2), clear viscous gel phase (Gel), multiphasic clear mixtures of gel phase dispersed in aqueous-based liquids (L_1+Gel) and multiphasic turbid mixtures (L_1+L_2) or (L_1+L_2+Gel).

In the case of formulation A in figure, 8; (Crodamol GTCC (18%), Glycerox 767HC (42%) and Etocas 35 HV (40%)), maximum solubilisation of water in the oil phase (L_2) occurred at 30% after which, transient phases could pass through Gel L_1+L_2+Gel L_1+L_2 L_1 phases. Yet, on the other hand, excluding Crodamol GTCC (medium chain triglyceride) from the lipid system as in formulation B (Glycerox 767HC (60%) and Etocas 35 HV (40%)), maximum solubilization of water as L_2 phase of around 50% is observed after which, o/w micro-emulsions (L_1) are formed.Equilibrium phase behavior on dilution with water for formulation C (Oleic Acid (12%), Crodamol PC (28%) and Etocas 35 HV (60%)) in figure 8 shows L_2 region at water concentration of 50% after which, transient phases could pass through L_1+ Gel L_1 phases. However, excluding oleic acid from the lipid system as in formulation D in figure 13; Crodamol PC (40%) and Etocas 35 HV (60%), though has shown similar L_2 region yet then, transient phases pass through L_1+L_2+Gel L_1+L_2 L_1 phases.

Effect of vehicle type on the fate of hydrophobic drug after dispersion

Photo depicted in figure 9 shows aqueous dispersion profiles for either lipid formulation composed of Crodamol GTCC (21%), Glycerox 767HC (49%) and Etocas 35 HV (30%) or PEG 400 co-solvent system containing Curcumin at concentration of 0.8mg/ml. Curcumin formulated in the self-micro-emulsifying lipid system produced clear dispersions with no sign of drug precipitation (photo   in figure 9; B). On the other hand, loss of solvency occurred for co-solvent based formulation which resulted in spontaneous precipitation of Curcumin (photo in figure 9; A).

DISCUSSION

Emulsification profiles of lipid formulations

Lipid systems containing medium-chain (C_8-C_{10}) triglyceride

An ideal SEDDS or SMEDDS should disperse into an emulsion or a microemulsion consisting of fine oil droplets in diameter with a uniform size distribution, to reduce the diffusion path of the drug from the droplet[1,15]. Such formulations will present a lipophilic drug in oily solution with a large interfacial area across which diffusion can take place. The mechanisms, rate and extent of drug absorption from the resulting dispersions will be strongly dependent on the oils and surfactants used in each formulation. For example, absorption will be influenced by whether or not the oil is digestible and by the partitioning of drug between the oil and water[16]. Lipids composed of long-chain triglycerides (LCT) or medium-chain triglyceride (MCT) are transported in the body by different mechanisms; MCT is directly transported by the portal blood to systemic circulation while, LCT stimulates the formation of lipoproteins, which facilitates their lymphatic transport[17].

The efficiency of SEDDS or SMEDDS depends on three main factors: particle size of oil droplets on exposure to aqueous media, rate of emulsification[18] and the polarity of the resulting oil droplets[1], which promotes partitioning of the drug into the aqueous phase. The polarity of the oil droplets is governed by the hydrophilic-lipophilic balance (HLB), the chain length and degree of un-saturation of the fatty acid, molecular weight of the hydrophilic portion and the concentration of the emulsifier[19].

SMEDDS on aqueous dispersion is able to form a microemulsion of droplets with diameters between 5and 140nm whereas for SEDDS, emulsions consisting of droplets <5μm in diameter are obtained. Hence, in the case of SMEDDS, dispersions can provide a relatively large interfacial surface area and hence results in faster drug release independent of the gastrointestinal physiology, digestion cascade and the fed / fasted state of the patient[20], provided the drug is maintained in solution in the GIT.

The narrow area of SMEDDS observed in systems containing Croduret 50 ss restricts the number of selected potential self-micro-emulsifying lipid formulation and hence makes this system less favorable to be considered from industrial perspective. Additionally, Croduret 50 ssis solid at room temperature and has a melting point of 30 C and hence any drop in the atmospheric temperature below 25 C shall induce crystallization of lipid matrix, which may lead to drug precipitation. On the

other hand, replacing Croduret 50 sswith Croduret 40 ssin the lipid mix widens the number of robust self-micro-emulsifying formulations that may be selected from the lipid system composed of Crodamol GTCC, Glycerox 767HC and Croduret 40 ss. This may suggest the fact that due to the polar characteristics of Corduret 40 ss as measured by its HLB value (13) has, from one hand, improved the mixing properties of the lipid pre-concentrate and moreover with Glycerox 767HC (HLB = 13.2) have produced oil droplets with a total HLB value that enhance degree of aqueous dispersion.Interestingly, self-micro-emulsiying dispersions can be obtained by blending a binary mix composed of Glycerox 767HC and Croduret 40 ss at only a 10% w/w minimum concentration of the non-ionic surfactant Croduret 40 ss, see line AB depicted on figure 4. Each of the lines AC, AD, AE and AF which are shown on figure 4 represents formulations at fixed ratio of Crodamol GTCC: Glycerox 767HC diluted with increasing concentration of Croduret 40 ss. Ratios of Crodamol GTCC: Glycerox 767HC for the representative formulations on lines AC, AD, AE and AF are 2:8, 3:7, 4:6 and 5:5, respectively. In order to obtain self-micro-emulsifying dispersions, minimum concentration of Croduret 40 ss (non-ionic surfactant) to be included in the binary mix of Crodamol GTCC and Glycerox 767HC at ratios of 2:8, 3:7, 4:6 and 5:5 (lines AC, AD, AE or AF) is approximately 18, 25, 30 or 40% w/w, respectively. This demonstrates that the progressive inclusion of Crodamol GTCC (source of triglyceride) in the lipid composite (i.e. moving from line AC to AF) entails gradual increase of the concentration of the non-ionic surfactant Croduret 40 ss to produce SMEDDS. Croduret 40 ss is a paste at room temperature which requires to be first melted when incorporated in the lipid mix hence, Etocas 35 HV which is liquid at room temperature with HLB value of 12.7 was selected as an alternative.Etocas 35 HV which is liquid at room temperature is considered to be a good alternative to Croduret 40 ss as it is capable to form stable lipid mixtures which readily emulsify in aqueous media forming micro-emulsion dispersions. Lipid composites presented in figures 3, 4 and 5 which have formed self-micro-emulsifying dispersions are considered archetypical examples of type III lipid class systems according to the classification of Pouten[5]. Therefore, 'Diffusion and Stranding' mechanism is considered to be the predominant process of emulsification of these lipid systems. The role of co-surfactant (Glycerox 767HC) in these lipid mixtures is to aid in the emulsification process by the virtue of its high polarity. It is thought that co-surfactant 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[21].

Lipid systems containing long-fatty acid chain (C_{16}-C_{18})

The narrow SMEDDS region for a lipid system composed of Olive oil (long chain triglycerides; LCT), Crodamol PC (co-surfactant) and Etocas 35 HV in comparison to lipid systems containing Crodamol GTCC (medium chain triglycerides; MCT) is in accordance with findings by Deckelbaum et al.[22] which had shown that in comparison to LCT, MCT are more soluble, have a higher mobility in the lipid/water interfaces and associated with a higher rate of hydrolysis by lipase. Furthermore, for the oil blend of {Oleic acid: Crodamol PC} of ratio 3:7 (line AB, figure 7), the minimum concentration of Etocas 35 HV included in the oil matrix to obtain self-micro-emulsifying systems is almost 55% w/w. Whereas, for oil blends containing MCT composed of (Crodamol GTCC: (Glycerox 767HC) at ratio of 3:7 (line AC, figure 5), optimum concentration of Etocas 35 HV to produce SMEDDS was only 30% w/w. In general, when usingLCT, a higher concentration of the surfactant is required to form micro-emulsions compared with MCT[23]. Sha et al.[24] developed a self-micro-emulsifying lipid formulation containing olive oil for the administration of probucoal (potent antioxidant and antihyperlipidemic agent) which dramatically enhanced bioavailability in an average of 2.15- and 10.22-fold that of oil solution and suspension, respectively.

From industrial perspective, selecting oleic acid in the lipid matrix is favored over olive oil due to the hetero-fatty acid composites of the latter. This is the case of Kaletra® (Lopinavir and Ritonavir, Abbott) which is formulated in a lipid mixture of oleic acid and polyoxyl 35 castor oil (Cremophor EL)[20].

It is important, however, to note here that self-microemulsifying drug delivery self-microemulsifying drug delivery systems (SMEDDS) based on long-chain (C18) lipids (LC-SMEDDS) significantly enhanced the oral bioavailability of danazol when compared to medium-chain (C8-C10) lipids (MC-SMEDDS)[25]. It was concluded that, despite displaying excellent dispersion properties, the susceptibility of MC-SMEDDS to lipase-mediated digestion has resulted in significant drug precipitation and hence little enhancement in danazol bioavailability occurred when compared with the long-chain lipid formulations. Highly lipophilic drug of log P > 5 included in long chain triglyceride at concentrations > 50mg/g may access the intestinal lymph via association with developing lipoprotein[26]. Therefore, since danazol is a highly lipophilic drug of log P 4.53, the subsequent incorporation of the long

chain fatty acids into the lipoprotein-dependent (chylomicron) lymphatic transport path has contributed to the superior bioavailability[25,26].

Nonetheless, this does not preclude, however, the importance of MC-SMEDDS in improving the bioavailability of lipophilic drugs, especially of log P between 2 and 5, as in the case of, Cyclosporine A (Neoral®, Novartis), Saquinavir (Fortovase®, Roche), Rapamycin[27], Ibuprofen[28] and Simvastatin[29]. The observed enhanced bioavailability of highly lipophilic drugs of log P > 5 incorporated in LC-SMEDDS relative to MC-SMEDDS[30,31] cannot though be generalized[17] as each drug behaves on its own merit in both systems. This is clear for Tipranavir (Aptivus®, BoehringerIngelheim Ltd) which has a log P of 6.9 and formulated as MC-SMEDDS composed of medium-chain mono and diglycerides mixed with Cremophor EL[32].

Effect of type of oil on the phase behavior of lipid mix

Self-emulsification is a dynamic non-equilibrium process which involves interfacial phenomena yet, investigating equilibrium phase behavior using static or dynamic compostion methods can give us an insight into the mechanistics of self-emulsification[33]. The role of co-surfactants (medium-chain mono/di-glycerides such as Imwitor 988) in the emulsification process of lipid formulations is thoroughly studied by Hasan[21]. He has found that incorporating optimum ratios of co-surfactant in the lipid matrix results in extensive enhancement in the water soubilisation region (L_2 phase; maximum solubilization capacity of water in the oil phase) and furthermore, causes the liquid crystalline materials to disappear from phase equilibrium diagrams. Therefore, co-surfactants in the lipid mix transform emulsification process from liquid crystalline involvement into "Diffusion and Stranding" process. Moreover, it is thought that a co-surfactant 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[21]. Nonetheless, the effect of oil type i.e. LCT's or MCT's which is included in the lipid matrix on the mechanistics of emulsification process is not thoroughly highlighted in literature.

It appears here that incorporating Crodamol GTCC (MCTs) in the lipid formulation,as in formulation A versus B in figure 8, impedes the emulsification process by restricting L_2 area, increasing number of transient phases before reaching o/w microemulsion (L_1 phase) and furthermore, decreasing total HLB of the lipid mix as Crodamol GTCC is a nonpolar oil with HLB of 1 to 3.

Nonetheless, although Crodamol GTCC, a medium chain triglyceride (MCT), appears to hamper emulsification process, paradoxically oleic acid (LCT) is found to aid emulsification process. Incorporating oleic acid in the lipid formulation (see formulations C and D in figure 8) appears to aid emulsification process by reducing the number of transient phases before reaching L_1 phase, and moreover, might be due to steric or ionic interaction effect as oleic acid is composed of long fatty acid (C18:1) which allows molecule to protrude at the oil water interface lowering the interfacial tension and thus increasing the interfacial fluidity. A study by Patel et al.,[34] formulating Lumefantrine (an important agent in the treatment of falciparum malaria) in a self-micro-emulsifying system composed of Oleic acid, Capmul MCM and Cremophore EL has shown oleic acid to aid emulsification thorough hydrophobic ionic complexion with the basic drug.

Effect of vehicle type on the fate of hydrophobic drug after dispersion

For the formulation design of successful self-micro-emulsifying key elements in the oil composite have to be optimized which include; type of oil, the use of co-surfactants, oil/co-surfactant ratio, the HLB of the surfactant and the inclusion of hydrophilic co-solvents[35]. Another key issue in the formulation design of lipid systems is to maintain solubility of the drug throughout its passage through the GI tract. Crystallization of the drug due to loss of solvent capacity of oil formulation on dilution in the lumen of the gut depends on the hydrophilicity of oil system; log *P* of the drug and the solubilization capacity of native surfactants (bile salt-lecithin mixed micelles) to maintain the drug in solution during digestion.

Nonetheless, the amount of oil (non-polar component) used in the lipid matrix is crucial in order to circumvent precipitation of the lipophilic drug after dispersion. In this case, the drug will be sequestered in the pool of the lipophilic core of the lipid matrix with minimal contact with the aqueous media. As a result, water's ability to "squeeze out" non-polar compounds is reduced and hence the rate of crystallization is retarded. In a study by Hasan[35] using a lipophilic dye (log P of 4.5) as a model drug has shown that the more hydrophilic a lipid vehicle is, the more susceptible to lose its solvent capacity on dispersion and thus more drug comes out of solution. Therefore, moving from Type I lipid class system to Type IV[5] increases hydrophilic nature of lipid vehicle and hence increases risk of drug precipitation in the lumen of the gut. Type IIIB and Type IV formulations generally produce the finest dispersions

because of their high content of water-soluble solubilizing agents. Hence, the water soluble components tend to diffuse away from the oil during dispersion, and become dissolved in the aqueous phase. The result of this separation, which may be the driving force for emulsification by 'diffusion and stranding', is likely to be loss of solvent capacity[18]. Furthermore, the inclusion of hydrophilic co-solvents such as PEG 400 at only 10-20% (w/w) in these systems accelerated DMY precipitation[35]. Similar finding were observed in a study by Mohsin[36] using Fenofibrate as a lipophilic model drug viz., significant drug precipitation was evident on dispersion and digestion of the representative Types of formulations from Type IIIB and IV systems.

In this investigation, Curcumin was selected as a lipophilic model drug of a log P of 3.28. In order to highlight the importance of vehicle type on the dispersion profiles of Curcumin, two systems one of which representing Type IIIA lipid formulation and a co-solvent based vehicle were selected. The solubility of Curcumin in either a lipid matrix composed of Crodamol GTCC (21%), Glycerox 767HC (49%) and Etocas 35 HV (30%), an archetypical Type IIIA system, or in a co-solvent based system of PEG400 was found ~ 80 and 145 mg/g lipid, respectively. Apparently, the solubility of Curcumin was relatively higher in PEG 400 as it has higher solubilization capacity.

Type IIIA lipid calls system composed of Crodamol GTCC (21%), Glycerox 767HC (49%) and Etocas 35 HV (30%) is considered a successful robust vehicle which is thought to mimic bioavailability of Curcumin. The system dispersion solvency is maintained and the drug is kept in solution. On the other hand, in the case of co-solvent based system, Curcumin precipitated out as microfine-structures, which is highly likely to occur in the lumen of gut, and as a result, bioavailability will be compromised.

Numerous publications have reported the significant pharmacodynamic activity of Curcumin (CRM) despite low or undetectable levels in plasma[37]. A study byWu et al.,[38] carried out on mice has shown that, formulating Curcumin in a Type IIIB lipid class system composed of 20% Isopropyl myristate as oil, 60% Cremophor RH40 as surfactant, and 20% ethanol as co-solvent has profoundly enhanced Curcumin bioavailablity vis-à-vis a suspension formulation. At a dose of 200 mg/kg, plasma level of curcumin was detected after 4 hours, the AUC0– , C_{max} and T_{max} values were 277.06 µg.h/L, 196.56 µg/L and 0.5 h, respectively[38]. Furthermore, a study on human volunteers by Pawre et al.,[37] has demonstrated that delivering Curcumin at a dose of 750mg in a more hydrophilic vehicle representing Type IV system consisted of (6.17% *w/w*)

Gelucire®44/14 (16.46% w/w), Labrasol (5.76% w/w), Vitamin E TPGS (3.29% w/w), PEG 400 (55.55% w/w), ethanol (8.23% w/w), anhydrous citric acid (2.88% w/w) and HPMC E5 (1.64% w/w) has also improved plasma levels of Curcumin. AUC0– , C_{max} and T_{max} values were found to be 321.12 ± 25.55 µg·h/L, 183.35 ± 37.54 µg/L and 0.60 ± 0.05 h, respectively.

CONCLUSION
Potential self-micro-emulsifying lipid formulations representing Type IIIA systems were developed for the oral administration of lipophilic drugs. Robust self-micro-emulsifying lipid systems were obtained using ternary oil blends composed of Crodamol GTCC as oil, Glycerox 767HC as co-surfactant and Crodurate 40ss as surfactant. Yet, due to the waxy nature of Crodurate 40ss which might restrict its industrial application, Etocas 35HV which is liquid at room temperature was found to be a potential substitute to Crodamol 40ss in the lipid matrix producing comparable self-micro-emulsifying profiles.

An archetypical Type IIIA micro-emulsion system composed of 21%w/w Crodamol GTCC, 49%w/w Glycerox 767HC and 30% w/w Etocas 35 HV was developed which can potentially mimic the bioavailability of Curcumin. This system at Curcumin concentration of 8% w/w emulsified in water producing micro-emulsion dispersions without losing solvent capacity of the lipid formulation and hence the drug is maintained in solution. On the other hand, co-solvent based formulation lost its solvency on dilution with water and thus Curcumin precipitated out as microfine structures which is likely to occur in the lumen of the gut.

Table 1
Typical Properties of Type I, II, III and IV Lipid Formulations [5].

	Increasing Hydrophilic Content				
	Type I	Type II	Type IIIA	Type IIIB	Type IV
Typical Composition (%) Triglycerides or	100	40 - 80	40 - 80	< 20	0
Surfactants	0	20 - 60 HLB <12	20 - 40 HLB > 12	20 - 50 HLB > 12	0 - 20 HLB < 12 20 - 80 HLB > 12
Hydrophilic Cosolvents	0	0	0 - 40	20 - 50	0 - 80
Particle Size of Dispersion (nm)	Coarse	100 - 250	100 - 250	50 - 100	<50
Significance of Aqueous Dilution	Limited Importance	Solvent Capacity Unaffected	Some Loss of Solvent Capacity	Significant Phase Change and Potential Loss of	Significant Phase Change and Potential Loss of Solvent
Significance of Digestibility	Crucial requirement	Not Crucial But Likely to Occur	Not Crucial But May be Inhibited	Not Required and Unlikely to happen	Not Required and Unlikely to happen

Table 2
Composition of the lipid formulations prepared for the phase behavior

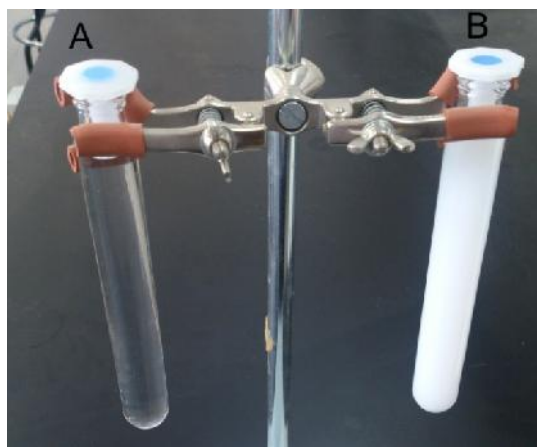| Formulation	Lipid		
	Crodamol GTCC	Glycerox	Etocas
A	18	42	40
B	0	60	40
	Lipid		
	Oleic Acid (% w/w)	Crodamol PC (% w/w)	Etocas (% w/w)
C	12	28	60
D	0	40	60

Figure 1
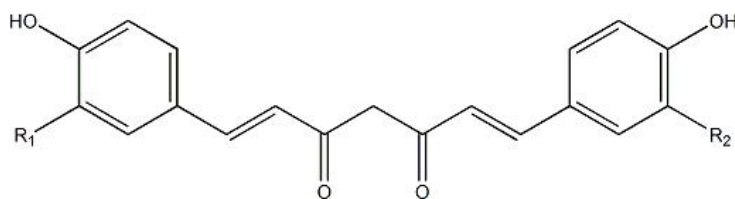**Photograph showing the difference between a microemulsion(A) and an ordinary emulsion (B).**

Figure 2
Chemical structure of Curcuminoids
1) R1 = R2 = OCH3 = Curcumin (Curcumin I).
2) R1 = OCH3, R2 = H = Demethoxycurcumin (Curcumin II).
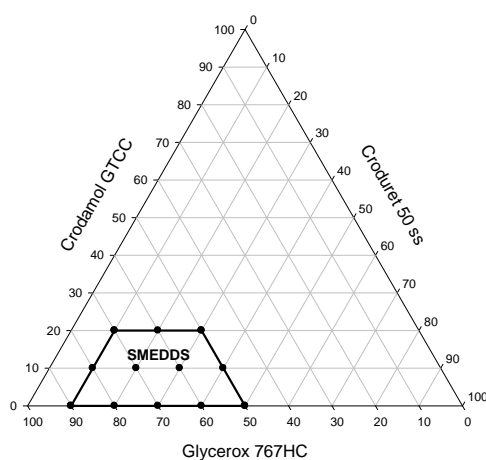**3) R1 = R2 = H= Bis-demethoxycurcumin (Curcumin III).**

Figure 3
Emulsification profile of a lipid system composed of Crodamol GTCC(oil), Glycerox 767HC (co-surfactant) and Croduret 50ss (non-ionic surfactant).
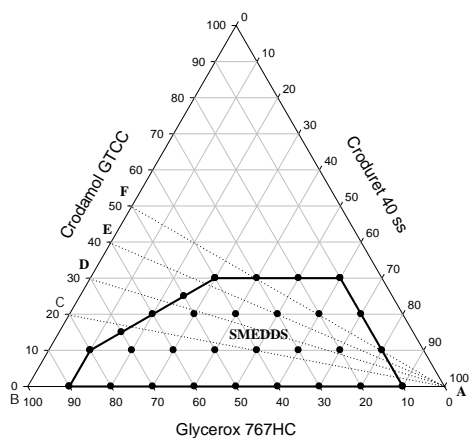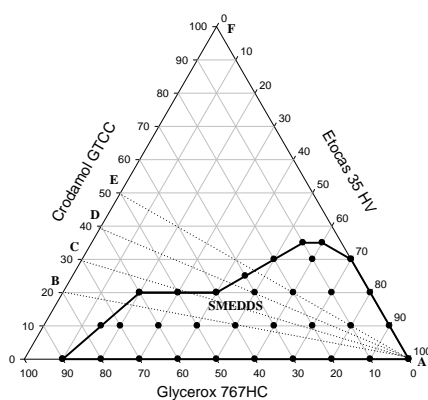

Figure 4
Emulsification profile of a lipid system composed of Crodamol GTCC(oil), Glycerox 767HC (co-surfactant) and Croduret40 ss (non-ionic surfactant).

Figure 5
Emulsification profile of a lipid system composed of Crodamol GTCC(oil), Glycerox 767HC (co-surfactant) and Etocas 35 HV (non-ionic surfactant).
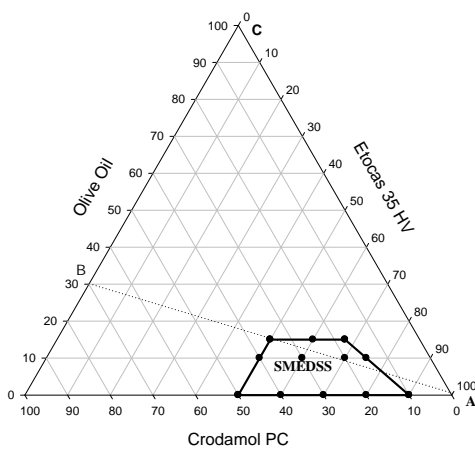

Figure 6
Emulsification profile of a lipid system composed of Olive Oil,Crodamol PC (co-surfactant) and Etocas 35 HV (non-ionic surfactant).
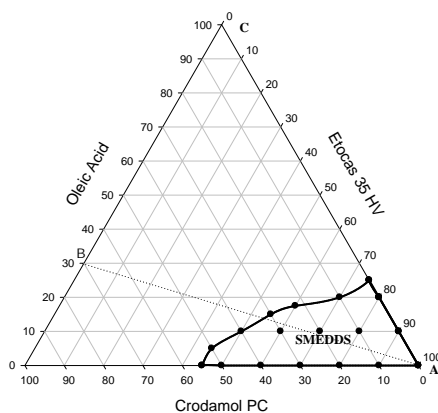

Figure 7
Emulsification profile of a lipid system composed of Oleic Acid,Crodamol PC (co-surfactant) and Etocas 35 HV (non-ionic surfactant).

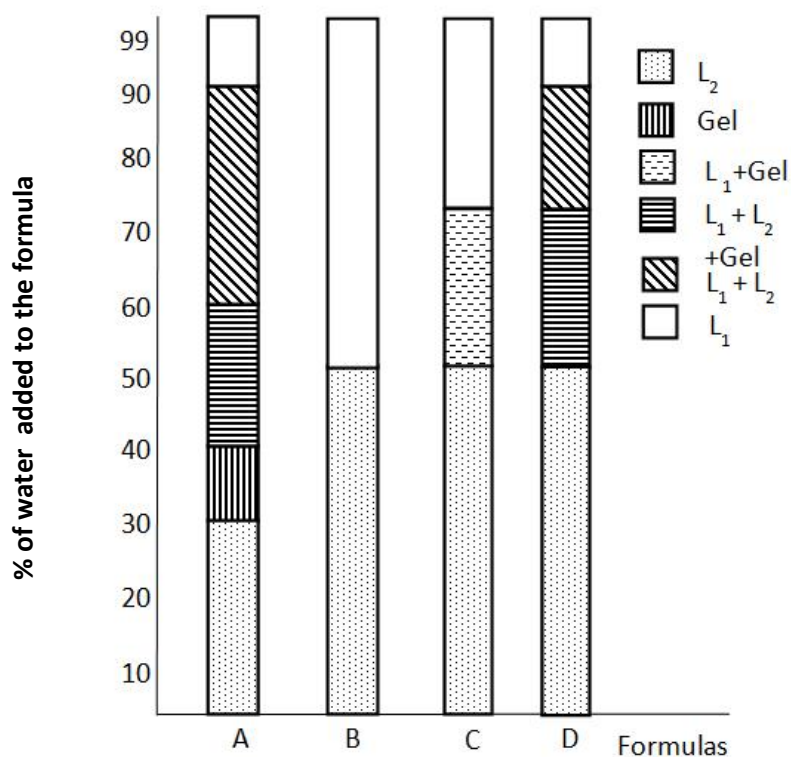**599**

Figure 8
Dynamic equilibrium phase behavior for various lipid systems with and without MCTs or LCTson sequential dilution with water.
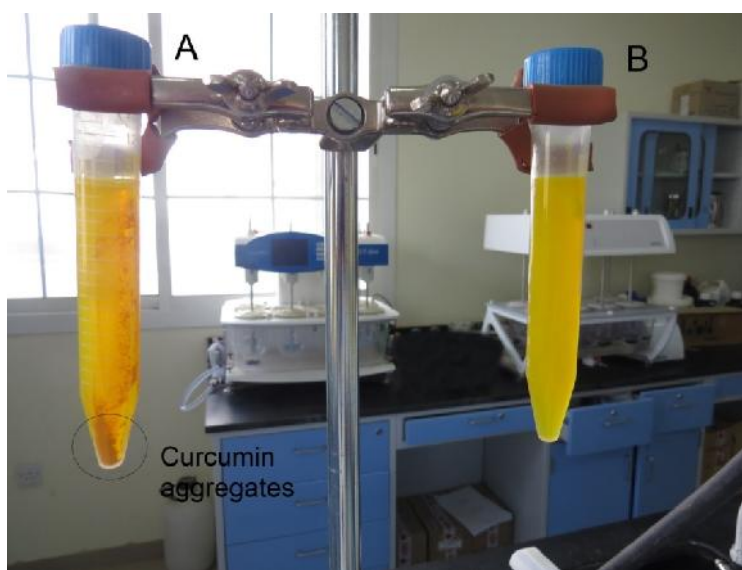

Figure 9
Photo shows aqueous dispersion profiles of Curcumin at concentration of 0.8mg/ml formulated in either SMEDDS {A} or PEG 400 co-solvent system{B}.

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