Research Article

# Studies on Drug Solubilization and Role of Lipid Vehicle in Pseudo Ternary Phase Diagram in Formulation Development of SNEDDS Containing Poorly Water Soluble Drug

**Milan D. Limbani*[1], L. D. Patel[2]**
[1]Ph.D. Scholar, Sharda School of Pharmacy, Pethapur, Gandhinagar, Gujarat, India.
[2]Director, Sharda School of Pharmacy, Pethapur, Gandhinagar, Gujarat, India.
***Corresponding author's E-mail:** milan_limbani@yahoo.com

**Accepted on:** 28-07-2016; **Finalized on:** 30-09-2016.

**ABSTRACT**

The purpose of this study was to select appropriate lipid vehicle and understand role of lipid vehicle in pseudo ternary phase diagram behaviour to find nanoemulsion area in formulation development of self nano emulsifying drug delivery system (SNEDDS) containing Fenofibrate and Atorvastatin Calcium. *In silico* prediction of drug solubility in a lipid vehicle remains challenging task. However, it has identified several factors that could be useful in predicting drug solubility in a particular excipient. These factors include the solubility parameter (δ), HLB value, partition coefficient, Molecular weight (MW), Dielectric constant (ε), dipole moment (μ) excipient fatty acid chain length, saponification value and viscosity. Non-ionic surfactant blends of Labrasol/Transcutol-P and Cremophor RH 40/Transcutol-P in different ratio were screened based on their solubilization capacity with water for Capmul MCM oil. High solubilization capacity was obtained by Cremophor RH 40/Transcutol-P (3:1) compared with other surfactant/co-surfactant ratio. High HLB blends of Cremophor RH 40/Transcutol-P (3:1) at HLB 12.3 has better solubilization capacity compared with the lower HLB values of Cremophor RH 40/Transcutol-P(2:1, 1:1) and Labrasol/Transcutol-P (3:1, 2:1, 1:1). All the selected blends of surfactants/co-surfactant were formed as oil-in-water microemulsions/nanoemulsion, and other dispersion systems varied in size and geometrical layout in the triangles. The high solubilization capacity and larger areas of the oil-in-water microemulsions/nanoemulsion systems were due to the structural similarity between the lipophilic tail of Cremophor RH 40 and the glycerides group of the Capmul MCM oil. This study also suggested that the pseudo ternary phase diagram behaviour of Capmul MCM oil, water, and non-ionic surfactant/co-surfactant is not affected by the HLB value.

**Keywords:** Solubility Parameter (δ), Pseudo ternary phase diagram, Capmul MCM oil, non-ionic surfactant/co-surfactant, SNEDDS, Microemulsion, Nanoemulsion.

## INTRODUCTION

An increasing number of recently discovered drug substances exhibit poor water solubility and hence low absorption after oral administration. An example of such a compound suffering from lower solubility and poor bioavailability are Fenofibrate, Atorvastatin, Pitavastatin, Simvastatin, etc.

Several strategies to improve the solubility and dissolution of such poorly water soluble drugs have been developed and described in literature like use of surfactants, lipids, permeation enhancer, micronization, salt formation, cyclodextrin complexation, nanoparticles, etc. Among these lipid base system the self nano emulsifying drug delivery system (SNEDDS) is promising technology to improve the dissolution rate and rate and extent absorption of poorly water soluble drugs.[1,2]

Nanoemulsion is a clear, isotropic, thermodynamically stable colloidal system which may be formed spontaneously by the chemical energy of surfactants, combinations of surfactants, and co-surfactants upon mixing a suitable oil phase and water without any mechanical energy input.[3,4] It has many advantages compared with conventional emulsions, including increased drug-loading and enhanced transdermal delivery.[4,5]

*In silico* prediction of drug solubility in a lipid vehicle remains challenging task. However, it has identified several factors that could be useful in predicting drug solubility in a particular excipient. These factors include the solubility parameter (δ), HLB value, partition coefficient, Molecular weight (MW), Dielectric constant (ε), dipole moment (μ) excipient fatty acid chain length, saponification value, surface tension and viscosity.

To the best of our knowledge, no information is available in the literature on the usefulness of solubility parameter, required HLB (RHLB), and required chemical type of emulsifiers or solubilization capacity for solubilising vehicles as criterion for the selection of surfactant/cosurfactant in the formulation development of SNEDDS using Fenofibrate or Atorvastatin Calcium.

The purpose of this study was to select appropriate lipid vehicle and to understand role of lipid vehicle in pseudo ternary phase diagram behaviour to find nanoemulsion area in formulation development of self nano emulsifying drug delivery system (SNEDDS) containing Fenofibrate or Atorvastatin Calcium.

Solubility Parameter (δ), Required HLB (RHLB), required chemical type of emulsifiers and Solubilization capacity appeared to be useful as a criterion for the selection of surfactant/co-surfactant.

The present study showed the importance of selecting a surfactant with the proper HLB for specific oils, as well as

the type of surfactant/co-surfactant. The solubility parameter (δ) of Fenofibrate and Atorvastatin Calcium are closest solubility parameter (δ) of Capmul MCM. Blend of better surfactant/co-surfactant was obtained when surfactant and co-surfactant at higher and lower HLB level respectively were blended. The greater the difference between the hydrophilic and lipophilic surfactants, the better the coverage by blends at the interface. The study also showed the importance of the structural similarities between the lipophilic tails of the surfactant blends. The pseudo ternary phase diagrams for mixtures of Capmul MCM oil with non-ionic surfactant/co-surfactant and water were constructed in this study.[6,7] The micelles discussed in this study have potential applications, advantages, and usefulness in the pharmaceutical industry as SNEDDS by various routes of administration, as well as in cosmetics and personal care products.[8,9]

## MATERIALS AND METHODS

### Materials

Labrasol and Transcutol-P were generous gift from Gattefose for research. Cremophor RH 40 was gifted from BASF. Capmul MCM oil was gifted from Abitech. Atorvastatin calcium was gifted from MSN. Fenofibrate was gifted from DIVI's Lab. All other chemicals used were of analytical grade.

### Methods

#### *Solubility Study*

Screening of solubilizing excipient was done by determining the solubility of Fenofibrate and Atorvastatin Calcium in different solubilizing vehicle like oils, surfactants and co-surfactants (Table 1). An excess quantity of Fenofibrate or/and Atorvastatin Calcium were added to the 2 ml of the solubilizing vehicle. Both components were mixed in a vial for 5 min using cyclomixer (REMI, Mumbai, India). The mixture in vial was shaken at 25 ± 1.0°C for 48 hour using controlled temperature rotary shaker. The mixtures were centrifuged using R-4C DX Laboratory Centrifuge (REMI, Mumbai, India) at 5000 rpm for 15 minute. The supernatant was separated and Fenofibrate and Atorvastatin Calcium were extracted in methanol. The drug content was analysed using Shimadzu 1700 UV-Visible spectrophotometer at 287 and 246 nm for Fenofibrate or Atorvastatin Calcium, respectively.

#### *Selection of Blend of Surfactant/Co-surfactant (Lipid Vehicle)*

Selection of surfactant is critical step in formulating the desired nanoemulsion. Each surfactant or oil has a specific HLB. The corrected HLB of the selected surfactant or blend of surfactant and co-surfactant that match the HLB of the selected oil provides the lowest interface tension between the oil and water phases. The HLB of the selected surfactant and blend of surfactant and co-surfactant reflects the stability of the system at lower levels, and can be obtained when the HLBs of the surfactant or blend of surfactant: co-surfactant and oil are similar.[10]

**Capmul MCM** is a mono-diglyceride of medium chain fatty acids (mainly caprylic and capric). It is an excellent solvent for many organic compounds including steroids.

**Polyoxyl 35 hydrogenated castor oil** is a non-ionic solubiliser and emulsifier made by reacting hydrogenated castor oil with ethylene oxide in a molar ratio of 1: 40. It has many uses as a nonionic surfactant, emollient, and thickening agent in skin preparations.

**Labrasol (Caprylocaproyl polyoxyl-8 glycerides)** is a non-ionic solubiliser and emulsifier. It is mixture of monoesters, diesters and triesters of glycerol and monoesters and diesters of polyethylene glycol with a mean relative molecular weight between 200 and 400. They are produced by partial alcoholysis of medium chain triglycerides with polyethylene glycol, by esterification of glycerol and polyethylene glycol with caprylic acid and capric acid, or as a mixture of glycerol esters and ethylene oxide condensate with caprylic acid and capric acid.

**Transcutol-P (Diethylene glycol monoethyl ether)** is non-ionic solubiliser and emulsifier. Structurally it is an alcohol and ether. It is a colorless, slightly viscous liquid with a mild pleasant odor.

Capmul MCM oil is composed of mono-diglyceride of medium chain fatty acids (mainly caprylic and capric) in which the side chains match the tail of non-ionic surfactant.

Therefore, non-ionic surfactants were chosen to study the phase diagram behaviour of Capmul MCM oil. Non-ionic surfactants are also recognized as being safe and biocompatible, and are not affected by pH changes in media because they are uncharged.

The non-ionic surfactants were chosen for screening to select a suitable blend of surfactant/co-surfactant that would best match Capmul MCM oil.

A blend of hydrophilic and lipophilic surfactants is needed to obtain longer stability of the dispersion phase at the lowest concentration levels.[11,12] A blend of surfactant/co-surfactant with an HLB that matches that of the oil phase will provide better solubilization and stability of the dispersion system produced. Therefore, the selection of surfactant blends at lower and higher HLB matching the HLB of oil is important in the formulation of a colloidal system.

#### *Calculation of Solubility Parameter*

Polarity of a solvent plays an important role in the solubility. Polar solvents are capable of solvating molecules through dipole interaction forces, particularly via hydrogen-bond formation, which is a major mechanism in the solubility of a compound. Polarity of solvents can be defined by dielectric constant (E), which is an important property related to the solubility and

hydrophilic-lipophilic balance.[13-16] It has been shown that the solubility of a solute decreased as the dielectric constant of solvent decreased.[17,18] An understanding of cohesive energy between drug and lipid molecules may help to determine how a lipid will behave as a solvent.

Cohesion is result of the London forces, polar interactions and specific ones like hydrogen bonding.[19,20] The commonly used approach in quantifying the cohesion between a solvent and a solute is the solubility parameter (δ), which is defined as the square root of the cohesive energy density, expressed as the energy of vaporization.

$$\delta = (CED)^{1/2} = (\Delta Ev/Vm)^{1/2} \quad \text{(Equation-1)}$$

Where CED is cohesive energy density ΔEv is the energy of vaporization and Vm is the molar volume.

This parameter may be useful to predict the solvating ability of a lipid or lipid mixture. When solubility parameters of lipid and drug are similar, they are expected to become miscible.[21, 2]

According to this calculation, the solubility parameter:

$$\delta_F = [\Sigma\Delta e/ \Sigma \Delta v]^{1/2} \quad \text{(Equation-2)}$$

Where Δe = the additive atomic group contributions for the energy of vaporization

Δv = the additive atomic group contributions for the molar volume

In this study, the group contribution method was used to calculate the solubility parameter from knowledge of the structural formula of the selected lipids and drug compounds.

Solubility parameters ($\delta_F$) of lipids and drugs were calculated using the group contribution method devised by Fedor's (Equation-2).

$$\delta_F = [\Sigma\Delta e/ \Sigma\Delta v]^{1/2} \quad \text{(Equation-2)}$$

In this mode the contribution of hydrogen bonding is not included. Therefore, hydrogen bonding contribution ($\delta_H$) was calculated as:

$$\delta_H = (5000m/V)^{1/2} \quad \text{(Equation-3)}$$

Where, m is the number of hydrogen donor and acceptors, and Vis the molar volume (MW/density).

Total solubility parameter ($\delta_T$) was calculated by adding hydrogen bonding contribution ($\delta_H$) to the Fedor's solubility parameter ($\delta_F$):

$$\delta_T = (\delta_F^2 + \delta_H^2)^{1/2} \quad \text{(Equation-4)}$$

Solubility parameters for Atorvastatin calcium and Fenofibrate were calculated by equation 4. Atorvastatin calcium has $\delta_{T\ (ATR)}$ of 15.27 $(cal/cm^3)^{1/2}$ and Fenofibrate has $\delta_{T\ (FENO)}$ of 16.46 $(cal/cm^3)^{1/2}$.

***Determination of Required HLB (RHLB) of Capmul MCM Oil***

To determine RHLB (o/w) for emulsification of Capmul MCM oil, a matched pair of surfactants belonging to same chemical class but having different hydrophilicity i.e. Cremophor RH 40 (non-ionic hydrophilic surfactant) and Transcutol-P (lipophilic surfactant) were selected. The batches of eleven surfactants blends, ranging in HLB from straight Cremophor RH 40 (HLB = 15) to Transcutol-P (HLB = 4.5) were shown in Table 2.

Eleven test formulation containing 25% Capmul MCM (oily phase), 75% water and one of the above surfactant/co-surfactant blend (10% of weight of Capmul MCM) were prepared in test tubes. Test tubes were closed using stopper. Test tubes were shaken once (up and down in a quick, hard motion) and observed for emulsification.

Similarly eleven test formulations were also prepared in beakers. Further, contents of each beaker were stirred for 1 minute using magnetic stirrer at 600 rpm, transferred in test tubes and observed for separation. The time taken by emulsion for separation of a particular volume of Capmul MCM was recorded. Trials were performed in triplicate. Required HLB for Capmul MCM was determined based on ease of preparation and time for separation. Number of times the test tubes shaken till a homogenous milky emulsion formed and time of separation for Capmul MCM emulsions prepared using emulsifiers of different HLB were shown in Table 3.

***Determination of required chemical type of Emulsifiers***

To find out appropriate surfactants, one more formulation was prepared using pair of Labrasol and Transcutol-P in such a ratio to give HLB value 12.84 (which is required for Capmul MCM). Ease of preparation and time for separation was determined and compared with the emulsion prepared using Cremophor RH 40 and Transcutol-P mixtures. Number of times the test tubes shaken till a homogenous milky emulsion formed and time of separation for Capmul MCM emulsion prepared using surfactant/co-surfactant blend of same HLB but different chemical type was shown in Table 4.

The individual non-ionic hydrophilic surfactant Labrasol and Cremophor RH 40 was blended with the lipophilic surfactant Transcutol-P in ratios of 1:1, 2:1, 3:1 w/w to produce blends of surfactant/co-surfactant with various HLBs in the range of 8.1–12.5.

***Measurement of solubilization capacity***

The water solubilization capacity, i.e, minimum content of non-ionic surfactant required to form a nanoemulsion system with Capmul MCM oil, was performed as a criterion for optimization using the water titration method.[23] The results of solubilization capacity were used to select the best emulsifier to study the phase diagram behaviour of Capmul MCM oil.

The blend of surfactant/co-surfactant forming a clear system at the minimum concentration (oil-in-water microemulsion/nanoemulsion) was selected as the blend that best matched the HLB of Capmul MCM oil.

### Construction of Pseudo-Ternary Phase Diagrams

Pseudo ternary phase diagrams were constructed based on the types of mixtures or dispersion systems formed when Capmul MCM oil-surfactant/co-surfactant mixtures were serially titrated with water at ambient temperature. Various weight to weight blends of selected surfactant/co-surfactant in the ratios of 1:1, 2:1 and 3:1 were produced to form surfactant/co-surfactant mixtures with HLB values of 8.1, 9.4, 10.1, 9.6, 11.4 and 12.3, respectively.[22]

The Capmul MCM oil and the blend of surfactant/co-surfactant at each HLB value were weighed separately in glass beakers, and were mixed and vortexed thoroughly in specific oil to surfactant/co-surfactant mixture ratios in the range of 0.25:4.75 – 4.5:0.5. Each mixture was slowly titrated with distilled water drop wise using a pipette. After each addition of water, the systems were vortexed for 10–20 seconds, and the final mixtures were vortexed for 2–3 minutes at room temperature. Initial visual observations of the resulting mixtures were categorized according to their physical characteristics. Microscopic examination was made of the final mixtures to identify the type of emulsion obtained using water-soluble dyes, i.e. Congo red and methylene blue. Details of the visual observation and microscopic identification of the resulting mixtures were recorded. The mixtures were stored for 24 hours at room temperature to achieve equilibrium. After equilibrium was reached, the final visual observation was recorded. The oil vertex in the triangle phase diagram represents Capmul MCM oil, the S/Cos vertex represents the surfactant/co-surfactant, and the remaining vertex represents the water phase.

To determine effect of drug addition on nanoemulsion boundary, phase diagrams were also constructed in presence of drug using drug-enriched oil as hydrophobic component. Phase diagrams were constructed using Tri plot v1-4 software.

## RESULTS AND DISCUSSION

### Solubility Study

Vehicles should have good solubilizing capacity for the drug substance, which is essential for formulating SNEDDS. The results of solubility of Fenofibrate and Atorvastatin Calcium in various vehicles were shown in Table 1. Fenofibrate and Atorvastatin Calcium had highest solubility in Capmul MCM Oil (Glyceryl Caprylate/Caprate) with comparison to other lipid vehicles. Fenofibrate and Atorvastatin Calcium had highest solubility in Cremophor RH 40 (Polyoxyl 40 hydrogenated Castor oil) and Transcutol-P as compare to other surfactant and co-surfactant. Capmul MCM Oil (Glyceryl Caprylate/Caprate) as oil, Cremophor RH 40 (Polyoxyl 40 hydrogenated Castor oil) as surfactant and Transcutol-P as co-surfactant were selected for optimal SNEDDS formulation resulting in improved drug loading capability. Furthermore, with respect to its safety, Capmul MCM Oil (Glyceryl Caprylate/Caprate), Cremophor RH 40 (Polyoxyl 40 hydrogenated Castor oil) and Transcutol-P are included in the FDA Inactive Ingredients Guide.

### Selection of Blend of Surfactant/Co-Surfactant

#### *Solubility Parameter (δ)*

Lipids used were better solvents for Atorvastatin calcium or Fenofibrate in increasing solubility because Atorvastatin calcium and Fenofibrate has higher lipophilicity with a log P of 5.7 and 5.3 respectively.

The solubility parameter calculated for Atorvastatin calcium is $\delta_{T\ (ATR)}$ = 15.27 $(cal/cm^3)^{½}$ (Table 5). Capmul MCM that has the closest solubility parameter (16.86 $(cal/cm^3)^{1/2}$) to that of Atorvastatin calcium and hence it provided the highest solubility among all lipids used. The same correlation could be observed with Fenofibrate. The calculated solubility parameter for Fenofibrate is $\delta_{T\ (FENO)}$ = 16.46 $(cal/cm^3)^{½}$ and the lipid that has closest solubility parameter is Capmul MCM (Capmul MCM = 16.86 $(cal/cm^3)^{1/2}$ (Table 5). Overall, calculated solubility parameter appeared to be a good predictor for the expected solvent effects of the lipids. The predictions are exclusively based on molecular structure of compounds, and no experimental data required.

#### *Required HLB (RHLB) of Capmul MCM Oil*

The data of Table-2 showed that among the surfactant/co-surfactant blends (Cremophor RH 40/Transcutol-P), the composition at 80:20 ratio having HLB 12.84 gave an emulsion that is easy to prepare and take longer time for separation of components then the other ten mixtures. These preliminary tests showed that the approximate RHLB for Capmul MCM is 12.84.

Under the HLB system, it was found that the oils, waxes, and other materials likely to be incorporated in to emulsion had an individual required HLB. This means that a surfactant or blend of surfactant/co-surfactant, having desired RHLB will make more stable emulsion than the emulsifier of any other HLB value.

#### *Required Chemical Type of Emulsifiers*

The mixture of Labrasol and Transcutol-P having HLB 12.84 gave similar results for ease of preparation and time for separation (no significant difference) as that of mixture of Cremophor RH 40 and Transcutol-P having similar HLB.

The 80:20 mixture of Cremophor RH 40 and Transcutol-P having HLB 12.84 was selected as surfactant/co-surfactant blend for further study.

#### *Solubilization Capacity*

Reverse micelle systems have been an interesting area of research in various fields of science and technology, due to their capability to solubilize water in organic solvent in the presence of surfactant.[25] It is known that ethoxylated non-ionic hydrophilic surfactants tend to form reverse micelles in organic media.[26] The results for the reverse micelle systems in this study formed by screening series

surfactants/co-surfactant were shown in Table 6. Cremophor RH 40/Transcutol-P (3:1) showed a high solubilization capacity compared with other S/CoS Ratio. Cremophor RH 40 (Polyoxyl 40 hydrogenated castor oil) is a non-ionic solubiliser and emulsifier made by reacting hydrogenated castor oil with ethylene oxide in a molar ratio of 1: 40.

Labrasol/Transcutol-P (1:1) showed the lowest solubilization capacity compared with Cremophor RH 40/Transcutol-P (3:1) (Table 6). This indicated a weak interaction between the oil and surfactant/co-surfactant from the same fatty acid derivative.

The results of this study were consistent with the study showing that the maximum solubilization capacity of water depends upon the oxyethylene chain and the configuration of the polar head group and hydrocarbon moiety of non-ionic surfactants and on type of oil.[23]

The results for the solubilization capacity of blends of surfactants/co-surfactant showed that Cremophor RH 40/Transcutol-P (3:1) at HLB 12.3 has the highest solubilization capacity compared with the Labrasol/Transcutol-P (3:1) at HLB 10.1. These results indicated the importance of the more lipophilic tail group that is structurally similar to the group on the Capmul MCM oil, which enables the co-surfactants to be well packed at the interface. Thus, these results reflected the effect of the type of co-surfactant blend on the solubilization capacity. The high solubilization capacity was obtained when surfactant/co-surfactant having the highest and lowest HLB value were mixed together, as shown by the solubilization capacity result for Cremophor RH 40/Transcutol-P (3:1) compared with the Labrasol/Transcutol-P (3:1) blend (Table 6).

The results of the study indicated the importance of selection of a better surfactant/co-surfactant blend showing strong solubilization capacity, which accordingly gives high stability.

**Pseudo Ternary Phase Diagrams**

Pseudo Ternary phase diagrams were constructed in presence of Fenofibrate or Atorvastatin Calcium to obtain optimum concentrations of oil, water, surfactant, and co-surfactant. SNEDDS formed fine oil–water emulsions with only gentle agitation, upon its introduction into aqueous media.

Phase behaviour investigations of this system demonstrated suitable approach to determining water phase, oil phase, surfactant concentration, and co-surfactant concentration with which transparent, one phase low-viscous nanoemulsion system was formed.[27]

Since free energy required to form an emulsion is very low, formation is thermodynamically spontaneous.[26] Surfactants form a layer around emulsion droplets and reduce interfacial energy as well as providing a mechanical barrier to coalescence. The visual test measured apparent spontaneity of emulsion formation.

Figure 1-2 presented the pseudo ternary phase diagram for mixtures of Capmul MCM oil, S/CoS (Labrasol/Transcutol-P and Cremophor RH 40/Transcutol-P) and water at various component compositions. All types of dispersions, including conventional water-in-oil and oil-in-water emulsions, water-in-oil and oil-in-water microemulsions, can be formed by S/CoS mixtures. A large area of clear isocratic solution (oil-in-water microemulsion/nanoemulsion) is formed at the oil-S/CoS axis in oil-rich regions. The minimum content of Cremophor RH 40/Transcutol-P (3:1) at an HLB of 12.3 formed in an isocratic system is 11.05% (fenofibrate) and 8.796% (Atorvastatin Calcium). This minimum content of surfactant/co-surfactant in a microemulsion or nanoemulsion system is known as the surfactant solubilization capacity.[23]

The smaller the percentage of S/CoS in a microemulsion/nanoemulsion system, the higher the solubilization capacity of the S/CoS, the better the match of the oil and S/CoS HLB, and hence the higher the stability of the product. Based on solubilization capacity, Cremophor RH 40/Transcutol-P (3:1) was selected as the best S/Cos.

The larger area of oil-in-water microemulsion/nanoemulsion formed by Cremophor RH 40/Transcutol-P (3:1) is due to the large molecular packing ratio of Cremophor RH 40/Transcutol-P, which is classified as a strong solubiliser.[29] Recent research has also suggested that the solubilization capacity and formation of oil-in-water microemulsion/nanoemulsion was caused by the extent of packing at the interface and not because of the HLB or the specific hydrophobicity of the surfactants.[26]

The main disadvantage of microemulsion/nanoemulsion systems is the lack of biocompatibility due to high surfactant(s) concentrations which might lead to toxicity or skin irritation.[30] Use of Capmul MCM oil that form a reverse micelle system in any formulation can overcome the lack of biocompatibility of such microemulsion/nanoemulsion systems because a low concentration of S/Cos is used.

Figures 1-2 showed the behaviours of surfactant/co-surfactant blends of Cremophor RH 40/Transcutol-P (with HLB values of 9.6, 11.3, and 12.3), Capmul MCM oil, and water at various concentration levels. The dispersion systems formed by these mixtures had reflected the nature and behaviour of their component compositions. The dispersion systems in these phase diagrams differ geometrically from Labrasol/Transcutol-P phase diagram. They showed much smaller areas of oil-in-water microemulsion/nanoemulsion compared with Cremophor RH 40/Transcutol-P (HLB 12.3). They also showed variation in area for the microemulsion system and other types of dispersion. Cremophor RH 40/Transcutol-P (3:1) at an HLB of 12.3 formed a large oil-in-water microemulsion/nanoemulsion area. The smaller area of oil-in-water microemulsion/nanoemulsion was due to a

lower HLB, which increases the lipophilic character of the surfactant blend.[31]

It was also clear from the solubilization capacity results that the Cremophor RH 40/Transcutol-P (3:1) with an HLB of 12.3 was a stronger solubiliser for water in Capmul MCM oil than other blends of Cremophor RH 40/Transcutol-P and Labrasol/Transcutol-P with HLB values in the range of 8.1–12.3. The weak interaction between the oil and S/CoS at lower HLB values for forming a reverse micelle system was due to the weaker solubilization of water at the interface in the presence of high percentages of lipophilic surfactant in the blends.

However, excessive amount of co-surfactant will cause system to become less stability for its intrinsic high aqueous solubility and lead to droplet size increasing as a result of expanding interfacial film.[32,33]

**Table 1:** Solubility of Fenofibrate and Atorvastatin Calcium in Various Oil, Surfactant and Co-Surfactant

| Material | Solubility (mg/ml) ± SD | |
|---|---|---|
| | Fenofibrate | Atorvastatin Calcium |
| Castor Oil | 72.18 ± 0.15 | 11.60 ± 0.06 |
| Labrafac PG | 58.85 ± 0.14 | 28.14 ± 0.04 |
| Oleic Acid | 21.43 ± 0.11 | 19.40 ± 0.10 |
| **Capmul MCM Oil** | **178.93 ± 0.38** | **52.97 ± 0.07** |
| Light Liquid Paraffin | 25.70 ± 0.12 | 10.69 ± 0.09 |
| Tween-80 | 74.80 ± 0.20 | 40.13 ± 0.04 |
| Span-20 | 47.22 ± 0.24 | 26.06 ± 0.07 |
| Labrafac Lipophile WL 1349 | 63.89 ± 0.22 | 42.02 ± 0.03 |
| Cremophor EL | 61.48 ± 0.18 | 30.43 ± 0.05 |
| **Labrasol** | **119.93 ± 0.46** | **74.48 ± 0.08** |
| Capmul GMO-50 | 36.29 ± 0.14 | 26.74 ± 0.08 |
| Captex 355 | 25.19 ± 0.08 | 14.31 ± 0.08 |
| PEG-400 | 36.39 ± 0.11 | 38.67 ± 0.07 |
| Propylene Glycol | 34.17 ± 0.11 | 10.74 ± 0.09 |
| **Transcutol-P** | **177.11 ± 0.43** | **82.28 ± 0.08** |
| **Cremophor RH 40** | **112.85 ± 0.31** | **71.32 ± 0.28** |

**Table 2:** Surfactant/Co-surfactant blends Cremophor RH 40 and Transcutol-P in different weight ratio and having different calculated HLB

| S. No. | Surfactant/Co-surfactant Blends | | Calculated HLB |
|---|---|---|---|
| | Cremophor RH 40 | Transcutol-P | |
| 1 | 100 | 0 | 15.00 |
| 2 | 90 | 10 | 13.92 |
| 3 | **80** | **20** | **12.84** |
| 4 | 70 | 30 | 11.76 |
| 5 | 60 | 40 | 10.68 |
| 6 | 50 | 50 | 9.60 |
| 7 | 40 | 60 | 8.52 |
| 8 | 30 | 70 | 7.44 |
| 9 | 20 | 80 | 6.36 |
| 10 | 10 | 90 | 5.28 |
| 11 | 0 | 100 | 4.20 |

**Table 3:** Number of times the test tubes shaken till a homogenous milky emulsion forms and time of separation for Capmul MCM emulsions prepared using emulsifiers of different HLB

| S. No. | Calculated HLB of Surfactant/co-surfactant blend | Number of times Test tubes shaken till a homogenous milky emulsion forms | | Time taken by emulsion for separation (min) | |
|---|---|---|---|---|---|
| | | Mean | SD | Mean | SD |
| 1 | 15.00 | 3.6 | 0.21 | 42.7 | 2.08 |
| 2 | 13.92 | 3.2 | 0.15 | 47.0 | 2.65 |
| 3 | **12.84** | **3.0** | **0.06** | **58.0** | **2.00** |
| 4 | 11.76 | 5.3 | 0.26 | 45.7 | 1.53 |
| 5 | 10.68 | 6.1 | 0.31 | 43.7 | 2.52 |
| 6 | 9.60 | 8.1 | 0.25 | 37.0 | 2.65 |
| 7 | 8.52 | 9.4 | 0.35 | 32.3 | 2.52 |
| 8 | 7.44 | 12.0 | 0.25 | 28.7 | 3.06 |
| 9 | 6.36 | 12.4 | 0.31 | 22.7 | 2.52 |
| 10 | 5.28 | 16.3 | 0.36 | 18.0 | 2.65 |
| 11 | 4.20 | No emulsification | | 2.3 | 0.58 |

**Table 4:** Number of times the test tube shaken till a milky emulsion forms and time for separation for Capmul MCM emulsion prepared using surfactant/co-surfactant blend of same HLB but different chemical type

| S. No. | Surfactant/Co-surfactant blend and HLB | Number of times the test tubes shaken for emulsification | | Time taken by emulsion for separation (min) | |
|---|---|---|---|---|---|
| | | Mean | SD | Mean | SD |
| 1 | Cremophor RH 40 and Transcutol-P, 12.84 | 3.0 | 0.06 | 58 | 2.00 |
| 2 | Labrasol and Transcutol-P, 12.84 | 4.0 | 0.25 | 51.3 | 1.53 |

**Table 5:** The Solubility Parameter of Selected Lipid Vehicles

| Materials | δH | Δv | δF | δT |
|---|---|---|---|---|
| **Atorvastatin Calcium** | **9.79** | **939.3** | **11.72** | **15.27** |
| **Fenofibrate** | **8.08** | **306.45** | **14.34** | **16.46** |
| **Capmul MCM Oil** | **11.74** | **217.81** | **12.10** | **16.86** |
| Light Liquid Paraffin | 7.03 | 405.12 | 7.62 | 10.36 |
| Castor oil | 7.81 | 982.56 | 5.34 | 9.46 |
| Oleic acid | 6.87 | 317.87 | 10.64 | 12.67 |
| Labrafac PG | 6.95 | 724.97 | 9.61 | 11.86 |
| Tween-80 | 10.77 | 560.01 | 8.73 | 13.87 |
| Span-20 | 11.58 | 335.72 | 6.34 | 13.20 |
| Labrafac Lipophile WL 1349 | 8.19 | 522.01 | 9.39 | 12.46 |
| Cremophor EL (Polyoxyl 35 castor oil) | 10.15 | 2233 | 9.77 | 14.09 |
| **Cremophor RH 40** | **10.40** | **2403.8** | **12.20** | **16.03** |
| **Labrasol** | **13.69** | **1094.3** | **6.68** | **15.23** |
| Capmul GMO-50 (Glyceryl Monooleate) | 8.88 | 380.19 | 12.10 | 15.01 |
| Captex 355 | 7.75 | 499.98 | 11.51 | 13.88 |
| PEG-400 | 12.99 | 355.56 | 6.14 | 14.37 |
| Propylene Glycol | 16.53 | 73.163 | 6.82 | 17.88 |
| **Transcutol-P** | **12.15** | **135.5** | **9.24** | **15.26** |

**Table 6:** The Solubilization Capacity of Selected Surfactants and Surfactant Blends

| Drug | Surfactant/Co-surfactant | HLB | Solubilization Capacity |
|---|---|---|---|
| Fenofibrate | Labrasol/Transcutol-P (1: 1) | 8.1 | 29.688 |
| | Labrasol/Transcutol-P (2: 1) | 9.4 | 23.750 |
| | Labrasol/Transcutol-P (3: 1) | 10.1 | 12.180 |
| | Cremophor RH 40/Transcutol-P (1: 1) | 9.6 | 27.457 |
| | Cremophor RH 40/Transcutol-P (2: 1) | 11.4 | 20.652 |
| | Cremophor RH 40/Transcutol-P (3: 1) | 12.3 | 11.050 |
| Atorvastatin Calcium | Labrasol/Transcutol-P (1: 1) | 8.1 | 12.838 |
| | Labrasol/Transcutol-P (2: 1) | 9.4 | 11.047 |
| | Labrasol/Transcutol-P (3: 1) | 10.1 | 9.694 |
| | Cremophor RH 40/Transcutol-P (1: 1) | 9.6 | 12.179 |
| | Cremophor RH 40/Transcutol-P (2: 1) | 11.4 | 10.106 |
| | Cremophor RH 40/Transcutol-P (3: 1) | 12.3 | 8.796 |

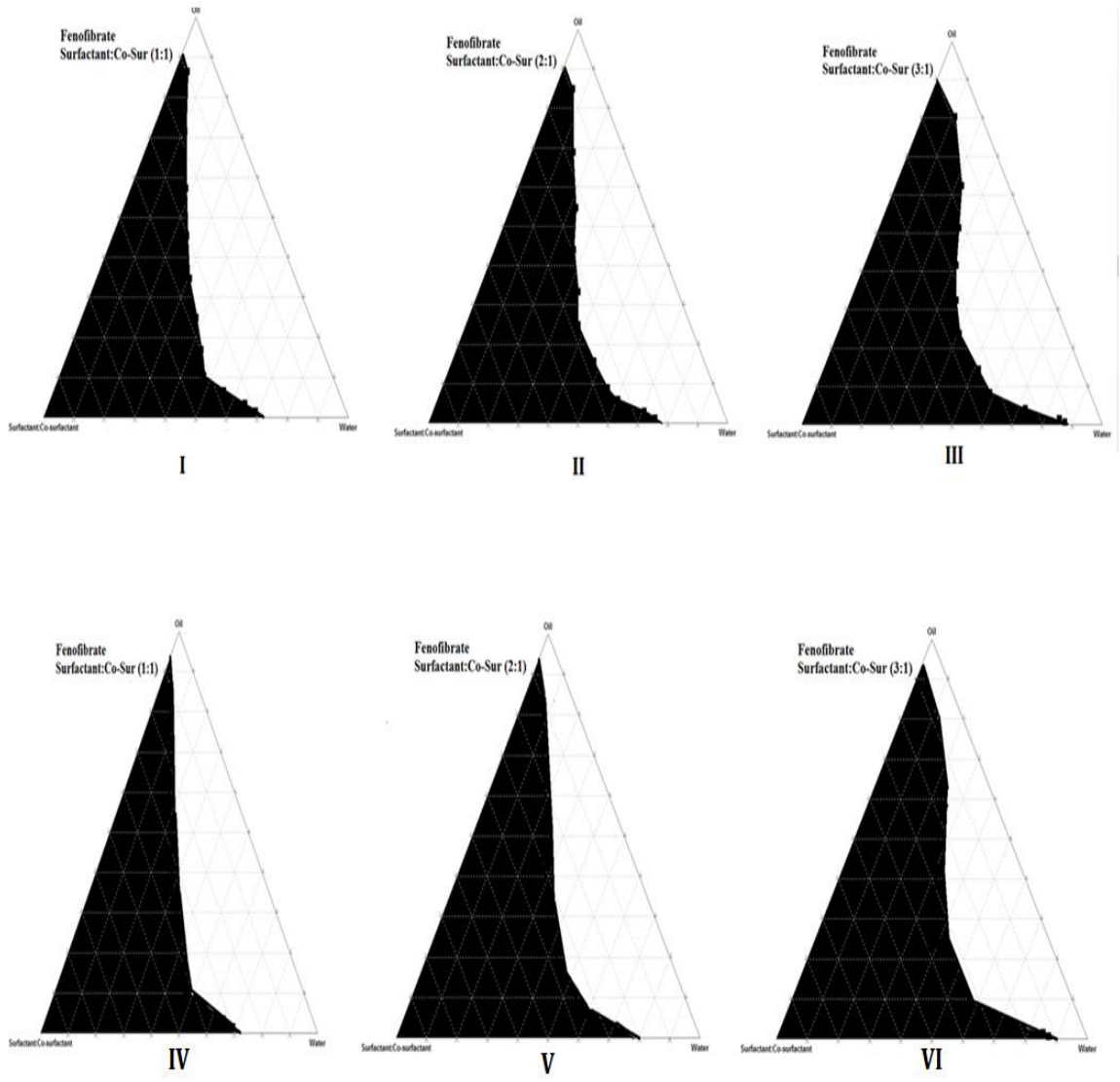


**Figure 1: (I)** S/Cos (Labrasol/Transcutol-P (1:1) at HLB - 8.1), **(II)** S/Cos (Labrasol/Transcutol-P (2:1) at HLB – 9.4), **(III)** S/Cos (Labrasol/Transcutol-P (3:1) at HLB – 10.1)**, (IV)** S/Cos (Cremophor/Transcutol-P (1:1) at HLB – 9.6), **(V)** S/Cos (Cremophor/Transcutol-P (2:1) at HLB – 11.3), **(VI)** S/Cos (Cremophor/Transcutol-P (3:1) at HLB – 12.3)

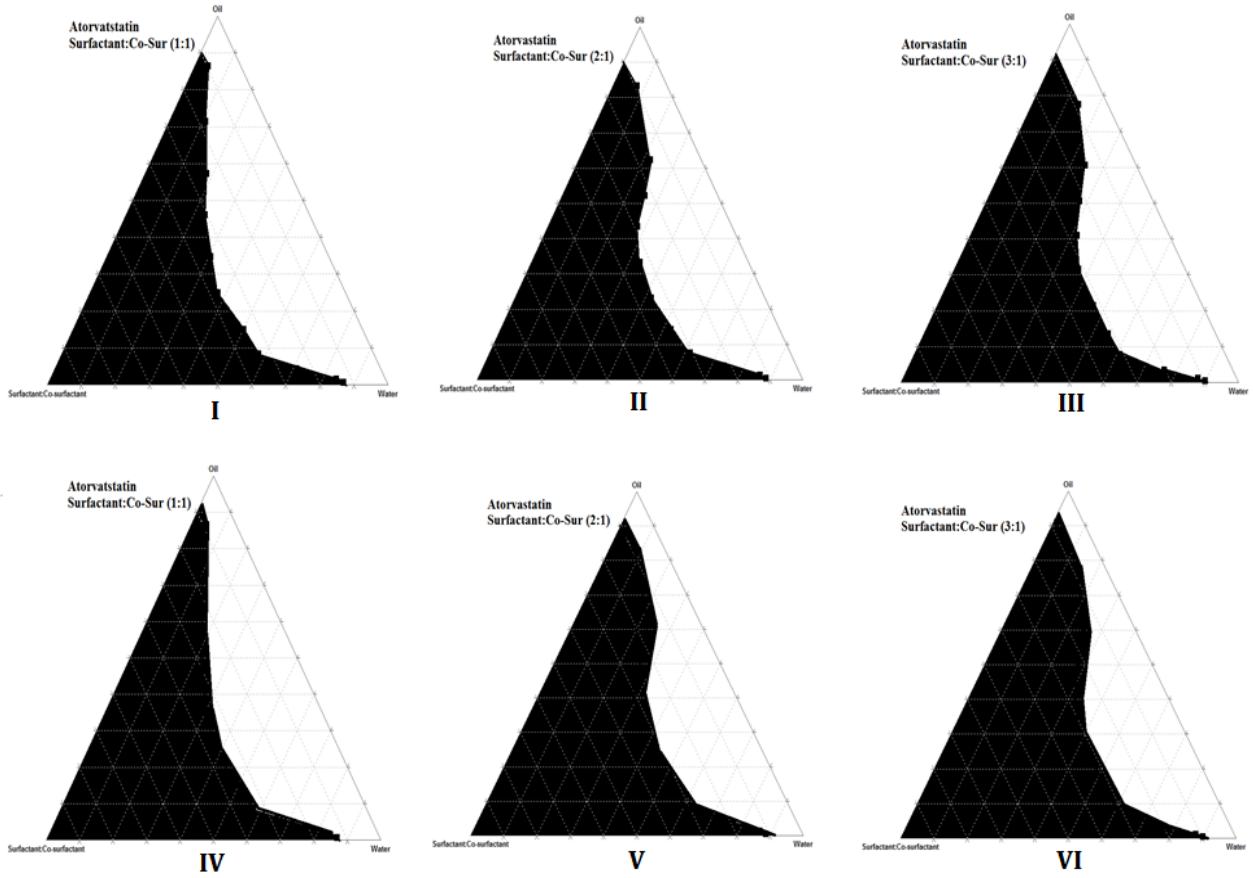


**Figure 2: (I)** S/Cos (Labrasol/Transcutol-P (1:1) at HLB - 8.1), **(II)** S/Cos (Labrasol/Transcutol-P (2:1) at HLB – 9.4), **(III)** S/Cos (Labrasol/Transcutol-P (3:1) at HLB – 10.1), **(IV)** S/Cos (Cremophor/Transcutol-P (1:1) at HLB – 9.6), **(V)** S/Cos (Cremophor/Transcutol-P (2:1) at HLB – 11.3), **(VI)** S/Cos (Cremophor/Transcutol-P (3:1) at HLB – 12.3)

## CONCLUSION

The purpose of the present was to select appropriate lipid vehicle and to understand role of lipid vehicle in pseudo ternary phase diagram behaviour to find nanoemulsion area in formulation development of self-nanoemulsifying drug delivery system (SNEDDS) containing Fenofibrate and Atorvastatin Calcium. Solubility Parameter (δ), Required HLB (RHLB), required chemical type of emulsifiers and Solubilization capacity were determined for selection of blend of surfactant/co-surfactant.

The pseudo ternary phase diagrams for mixtures of Capmul MCM oil with non-ionic surfactant/co-surfactant and water were constructed in this study. The present study showed the importance of selecting a surfactant with the proper HLB for specific oils, as well as the type of surfactant/co-surfactant. The solubility parameter (δ) of Fenofibrate and Atorvastatin Calcium are closest solubility parameter (δ) of Capmul MCM. Blend of better surfactant/co-surfactant was obtained when surfactant and co-surfactant at higher and lower HLB level respectively were blended. The greater the difference between the hydrophilic and lipophilic surfactants, the better the coverage by blends at the interface. The study also showed the importance of the structural similarities between the lipophilic tails of the surfactant blends.

The SNEDDS have potential applications, advantages, and usefulness in the pharmaceutical industry as SNEDDS by various routes of administration, as well as in cosmetics and personal care products. Solubility Parameter (δ), Required HLB (RHLB), required chemical type of emulsifiers and Solubilization capacity appeared to be useful as a criterion for the selection of surfactant/co-surfactant along with pseudo ternary phase diagrams in formulation development of SNEDDS.

**Acknowledgement:** We are thankful to Respected Learned Professors Dr. M.C. Gohel and Dr. (Mrs.) Krutika Sawant and Dr. Manish A. Rachchh for their important guidance and suggestions in achieving the outputs of the results of present research work.

## REFERENCES

1. Singh SK, Verma PRP, Razdan B. Development and characterization of a lovastatin loaded self-micro emulsifying drug delivery system. Pharm. Develop. and Tech., 15, 2010, 469-83. DOI: 10.3109/10837450903286537
2. Hong JY, Kim JK, Song YK, Park JS, Kim CK. A new self-emulsifying formulation of itraconazole with improved dissolution and oral absorption, J. Contr. Release, 110, 2006, 332-8. DOI: 10.1016/j.jconrel.2005.10.002
3. Hauss DJ, Fogal SE, Ficorilli JV, Price CA, Roy T, Jayaraj AW, Keirns JJ. Lipid-based delivery systems for improving the bioavailability and lymphatic transport of a poorly water-soluble LTB4 inhibitor, J Pharm Sci., 87(2), 1997, 164–169.

4. Strickley RG. Currently marketed oral lipid-based dosage forms: Drug products and excipients and Lipid-based formulations for oral delivery: Enhancing bioavailability of poorly water-soluble drugs, Informa Healthcare, New York, 2007, 1–31.
5. Porter CJH, Trevaskis NL, Charman WN. Lipids and lipid-based formulations: Optimizing the oral delivery of lipophilic drugs, Nature Rev., 6, 2007, 231–48. DOI: 10.1038/nrd2197
6. Shafiq-un-Nabi S, Shakeel F, Talegaonkar S. Formulation development and optimization using nanoemulsion technique: A technical note, AAPS Pharm Sci Tech., 8(2), 2007, 12–17. DOI: 10.1208/pt0802028
7. Sadoqi M, Lau-Cam CA, Wu SH. Investigation of the micellar properties of the tocopheryl polyethylene glycol succinate surfactants TPGS 400 and TPGS 1000 by steady state fluorometry, J Colloid Interface Sci, 333(2), 2009, 585–589.
8. Yaghmur A, Campo L, Aserin A, Garti N, Glatter O. Structural characterization of five-component food grade oil-in-water nonionic microemulsions, Phys Chem Chem Phys., 6(7), 2004, 1524–1533.
9. Yuan Y, Li SM, Mo FK, Zhong DF. Investigation of microemulsion system for transdermal delivery of meloxicam, Int J Pharm., 321(1–2), 2006, 117–123. DOI: 10.1016/j.ijpharm.2006.06.021
10. Zhang P, Liu Y, Feng N, Xu J. Preparation and evaluation of self-microemulsifyig drug delivery system of oridin, Int J Pharm., 355, 2008, 269–276. DOI: 10.1016/j.ijpharm.2007.12.026
11. Jiao J, Burgess D. Rheology and stability of water-in-oil-in-water multiple emulsions containing Span 83 and Tween 80, AAPS J., 5(1), 2003, 62–73.
12. Golemanov K, Tcholakova S, Denkov N, Gurkov T. Selection of surfactants for stable paraffin-in-water dispersions, undergoing solid-liquid transition of the dispersed particles, Langmuir, 22(8), 2006, 3560–3569.
13. Gorman WG, Hall GD. Use of dielectric constant in the classification of surfactants, Journal of Pharmaceutical Sciences, 52(5), 1963, 442-446. DOI:10.1002/jps.2600520508
14. Gorman WG, Hall GD. Dielectric constant correlations with solubility and solubility parameters, Journal of Pharmaceutical Sciences, 53(9), 1964, 1017-1020.
15. Cave G, Puisieux F, Carstensen JT. Dielectric constants of solid-liquid and liquid-liquid systems as a function composition, Journal of Pharmaceutical Sciences, 68(4), 1979, 423-426.
16. Rabaron A, Cave C, Puisieux F, Seiller M. Physical methods for measurement of the HLB of ether and ester non-ionic surface-active agents: HNMR and dielectric constant, International Journal of Pharmaceutics, 99, 1993, 23-36.
17. Carstensen JT. Dielectric constants of solid-liquid and liquid-liquid systems as a function composition, Journal of Pharmaceutical Sciences, 68(4), 1979, 423-426.
18. Trivedi JS, Porter WR, Fort JJ. Solubility and stability characterization of zileuton in a ternary solvent system, European Journal of Pharmaceutical Sciences, 4, 1996, 109-116. DOI: 10.1016/0928-0987(95)00038-0
19. Hansen C, Beerbower A. Solubility parameters, Encycl. Chem. Technol., 2nd Ed, edited by Standen A, Interscience, New York, 1971, 889-910.
20. Barton AFM. Solubility parameters, Chemical Reviews, 75(6), 1975, 731-753.
21. Scatchard G. Equilibria in non-electrolyte solutions in relation to the vapor pressures and densities of the components, Chemical Reviews, 8(2), 1931, 321-333.
22. Krevelen VDW, Hoftyzer PJ. Properties of polymers correlation with the chemical structure, Elsevier Publishing Company, New York, 85-107, 1972, 135-143.
23. Förster T, Von Rybinski W, Wadle A. Influence of microemulsion phases on the preparation of fine-disperse emulsions, Adv Colloid Interface Sci., 58(2–3), 1995, 119–149.
24. Li P, Ghosh A, Wagner RF, Holinej J, Krill S, Joshi YM, Serajuddin ATM. Effect of combined use of nonionic surfactant on oil-in-Water microemulsions, Int. J. Pharm., 288(1), 2005, 27–34. DOI: 10.1016/j.ijpharm.2004.08.024
25. Paul BK, Mitra RK. Water solubilization capacity of mixed reverse micelles: Effect of surfactant component, the nature of the oil, and electrolyte concentration. J Colloid Interface Sci., 288(1), 2005, 261–279.
26. Porras M, Solans C, González C, Gutiérrez JM. Properties of water-in-oil (W/O) nano-emulsions prepared by a low-energy emulsification method. Colloids Surf A Physicochem Eng Asp., 324(1–3), 2008, 181–188.
27. Haroon KS, Kok KP. Identification of Phases of Various Oil, Surfactant/Co-Surfactants and Water System by Ternary Phase Diagram, Acta Poloniae Pharmaceutica-Drug Research, 71(2), 2014, 301-309.
28. Craig DQM, Barker SA, Banning D, Booth SW. An investigation into the mechanisms of self-emulsification using particle size analysis and low frequency dielectric spectroscopy. Int. J. Pharm., 114, 1995, 103–110.
29. Sjöblom J, Lindberg R, Friberg SE. Microemulsions – phase equilibria characterization, structures, applications and chemical reactions, Adv Colloid Interface Sci., 65, 1996, 125–187. DOI:10.1016/0001-8686(96)00293-X
30. Alany RG, Rades T, Nicoll J, Tucker IG, Davies NM. W/O microemulsions for ocular delivery: Evaluation of ocular irritation and precorneal retention, J Control Release, 111(1–2), 2006, 145–152. DOI: 10.1016/j.jconrel.2005.11.020
31. Kunieda H, Solans C, Shida N, Parra J. The formation of gel-emulsions in a water/nonionic surfactant/oil system, Colloids Surf., 24(2–3), 1987, 225–237. DOI: 10.1016/0166-6622(87)80352-9
32. Lawrence MJ, Rees GD. Microemulsion-based media as novel drug delivery systems, Adv. Drug Del. Rev., 45, 2000, 89–121. PMID: 11104900
33. Zhang QZ, Jiang XG, Jiang WM, Lu W, Su LN, Shi ZQ. Preparation of nimodipine-loaded microemulsion for intranasal delivery and evaluation on the targeting efficiency to the brain, Int. J. Pharm., 275, 2004, 85–96. DOI: 10.1016/j.ijpharm.2004.01.039


**Source of Support:** Nil, **Conflict of Interest:** None.

**Corresponding Author's Biography : Mr. Milan D. Limbani**

Mr. Milan D. Limbani is graduated from Saurashtra University, India and Post graduate from Department of Pharmaceutical Sciences, Saurashtra University. At post graduation level taken specialization in Pharmaceutics, completed master thesis in "Preparation and *In vivo* Evaluation of Self Nano emulsifying Drug Delivery System (SNEDDS) Containing Ezetimibe". Currently work in Pharmaceutical Research center and as Ph.D. scholar in Sharda school of Pharmacy.