ABSTRACT
BACKGROUND: Curcumin is poorly permeable as well as sparingly soluble drug with varying interpersonal and intrapersonal bioavailability. The main purpose of present work was to develop self Microemulsifying drug delivery system (SMEDDS). Preliminary trials were performed using various oils and surfactants. Pseudo-ternary phase diagrams were constructed to identify the efficient self-emulsification region. The formulation of Curcumin SMEDDS was optimized by a simplex lattice design. The optimal formulation of SMEDDS was comprised of 15% oil (Pecol:Ethyl oleate in 1:1 ratio), 50% surfactant (Labrasol) and 35% co-surfactant (Cremophor EL). The average globule size of optimized SMEDDS containing drug was about 36 nm when diluted in water. No significant variations in globule size and Curcumin content in SMEDDS were observed over a period of 3 months at 40 ±2°C/75 ± 5% RH and 25 ± 3°C (room temperature). In vitro diffusion studies of optimized batch using dialysis membrane technique showed more than 95% drug diffusion within 15 min. The data suggested the use of SMEDDS to provide great potential for delivery of Curcumin.

Key Words: Curcumin, Diffusion, Optimization, SMEDDS, Stability

INTRODUCTION
The fundamental step in the solubilisation of drug compounds is the selection of an appropriate salt form, or for liquid dosage forms, adjustment of pH of the solution. This is an especially important selection process for polar compounds as the majority of newer solubilisation techniques such as nanosuspensions and microemulsions utilize co-solvents when applied to a polar compound. These technologies include both traditional methods of solubility enhancement, such as particle size reduction via comminution, spray drying, addition of surfactants, inclusion in cyclodextrin-drug complexes, and the use of more novel mechanisms such as self-emulsifying systems, micronisation via nanoparticles, pH adjustment and salting-in processes.

Microemulsions and self-emulsifying systems have emerged as potential solubility enhancing technologies, whose solubilising and absorption promoting effect is thought to lay in the reactivity of triglycerides and surfactants with the walls of the gastrointestinal tract. Traditionally, long and medium-chain triglycerides (LCTs and MCTs, respectively) have been employed with surfactants to incorporate drugs into self-emulsifying systems. Non-ionic surfactants, such as Tweens (polysorbates) and Labrafil (polyoxyethylated oleic glycerides), with high hyrophile-lipophile balances (HLB) are often used to ensure immediate formation of oil-in-water (o/w) droplets during production. Amphiphilic, non-ionic surfactants allow higher degrees of drug solubilisation to occur and may prevent the precipitation of drug out of the microemulsion in vivo. Co-surfactants are frequently employed to increase the amount of drug capable of being dissolved into the lipid base, because the concentration of surfactant in most self-emulsifying systems is required to be in excess of 30% w/w. These co-surfactants are often organic solvents suitable for oral administration, such as ethanol, propylene glycol and poly ethylene glycol. Similar to the impact of introducing organic solvents elsewhere in drug product manufacture, the use of co-solvents increases processing complexity while improving the potential drug load of the emulsion. Most self-emulsifying systems are...
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limited to administration in lipid-filled soft or hard-shelled gelatin capsules due to the liquid nature of the product. Interaction between the capsule shell and the emulsion should be considered so as to prevent the hydrosopic contents from dehydrating or migrating into the capsule shell. Curcumin, a naturally active constituent extracted from the plants of the Curcuma longa, its structure shown in Figure 1. Curcumin is the principal curcuminoid of the popular Indian spice turmeric which belongs to the ginger family (Zingiberaceae). It has a variety of biological activities and pharmacological actions, such as anti-tumor, anti-inflammatory, anti-virus, anti-oxidation and anti- HIV, and low toxicity with promising clinical application 6,7 which have low oral bioavailability i.e. 40-85% of an oral dose of Curcumin passes through the gastrointestinal tract unchanged, with most of the absorbed flavonoid being metabolized in the intestinal mucosa and liver8.

In present study SMEDDS of curcumin was prepared for enhanced solubility and dissolution of poorly soluble drug.

Figure: 1 Structure of Curcumin.

MATERIAL AND METHODS
Curcumin was received as a generous gift sample from Konark Herbals And Health Care, Daman, Gujarat., Ethyl oleate was gifted by Central drug house., India. Cremophore EL was gifted by BASF India Ltd. Mumbai., India, Pecoe & Labrasol were gifted by Gattefosse India PvtLtd.Mumbai. and other chemicals and reagents used were of analytical grade.

Solubility Studies9
The solubility of curcumin in various oils, surfactants, co-surfactants and Oil; surfactant mixture was measured using shake flask method 8-12. An excess amount of curcumin was added into each vehicle followed by vortex mixing for 30 sec. Mixtures were shaken for 48 hr at 30°C in a thermostatically controlled shaking water bath, followed by equilibrium for 24 hr. Mixtures were then centrifuged at 3000 rpm for 10 min and the supernatant was filtered through a Millipore membrane filter (0.45µ). Samples were suitably diluted with methanol and drug concentration was obtained via UV validated method at 432 nm using hydro alcoholic solvent (Methanol: Distilled Water. 3:7) as a blank. The experiment was repeated in triplicates. Results are represented as mean value (mg/ml) ± SEM.

Preliminary screening of surfactant 10
Different surfactants for the peroral use were screened for emulsification ability. Briefly, Excess amount of drug in 5ml of selected oils was taken in stopper vials and was then mixed by vortex mixer. The mixture vials were then kept at 37±2°C in an isothermal orbital shaker for 72 hr to reach equilibrium. The equilibrated samples were removed from shaker and centrifuged at 5000 rpm for 15 min. The solubility profile of drug in oil was determined from the supernatant using UV-VIS spectrophotometer at 432 nm. Insoluble drug from the settled material was determined and mass balance was then found out. HLB value, drug solubility, biocompatibility and compatibility with drug are the parameters evaluated in the selection of surfactant. Since the formulation to be developed was o/w microemulsion, surfactants having HLB value ranges between 8 to15 were first screened followed by drug solubility as described earlier.

Phase diagram Study
In pseudoternary phase diagrams of curcumin based micro emulsion were prepared by Tri Plot Version 4.1.2 software. To determine effect of drug addition on Microemulsion boundary, phase diagrams were also constructed in presence of drug using drug-enriched oil as hydrophobic component.

Formulation of SMEDDS
A series of SMEDDS formulations were prepared using Labrasol and CremophorEl as Surfactant/Co-surfactant combination and Pecoe & Ethyl oleate (in ratio of 1:1)
as oil by using Simplex Lattice Design. The actual concentrations of oil, surfactant and co-surfactant were transformed based on the simplex lattice design so that minimum concentration corresponds to zero and maximum concentration corresponds to one (Shown in Table 1). Briefly, accurately weighed curcumin was placed in a glass vial, and oil, surfactant, and cosurfactant were added. Then the components were mixed by gentle stirring and vortex mixing on a magnetic stirrer, until curcumin was perfectly dissolved. The mixture was stored at room temperature until further use.

**Formulation optimization**

A simplex lattice experiment design was used to optimize composition of Microemulsion (SMEDDS). In this design, three factors were evaluated by changing their concentrations simultaneously and keeping their total concentration constant. The simplex lattice design for three-component system is represented by an equilateral triangle (shown in Figure 2).

Seven batches of SMEDDS were prepared, including three vertexes (A, B, C), three half-way points between vertices (AB, AC, BC), and one centre point (ABC). The concentrations of surfactant, co-surfactant and oil were selected as independent variables. The responses for seven formulations were used to fit an equation for simplex lattice model which then can predict properties of all possible formulations. With the aid of software (Design expert 8.0.5.), the model equation was developed to represent the relationship between the Mean globule size, percentage transparency and amount of curcumin diffuse and the measured characteristics.

**Figure 2 : Equilateral triangle representing simplex lattice design For three components**

**Evaluation of SMEDDS**

**Self Emulsification and Phase Separation:**

Different compositions were categorized on speed of emulsification, clarity, and apparent stability of the resultant emulsion. Visual assessment was performed by drop wise addition of the preconcentrate (SMEDDS) into 100, 250 and 1000 mL of distilled water, 0.1N HCl and pH 6.8 phosphate buffer. This was done in a glass beaker at room temperature, and the contents were gently stirred with glass rod. Precipitation was evaluated by visual inspection of the resultant emulsion after 24 hours. The formulations were then categorized as clear (transparent), non clear (turbid), stable (no precipitation at the end of 24 hours), or unstable (showing precipitation within 24 hours).

**Droplet Size**

Particle size of emulsion was determined by using dynamic light scattering technique by Malvern zetasizer (NANO ZS). Samples were diluted to 50 times and 100 times with the Distilled water for the measurement.

**Drug Content**

The SMEDDS containing curcumin was measured using UV visible spectroscopic method. The 2 µg/ml of aliquot was prepared using microemulsion formulation using diluting solvent. The samples were measured as 432 nm using UV-VIS spectroscopic method.

**In-Vitro Diffusion Studies:**

In vitro diffusion studies were carried out for all formulations using dialysis technique. One end of pre-treated dialysis membrane tubing (12 cm in length) was with thread and then diluted of self Microemulsifying formulation was filled in it. The other end of tubing was also secured with thread and was allow to rotate freely in dissolution vessel of USP paddle type II dissolution test apparatus (Electrolab TDT-08L, USP) that contained 250 ml dialyzing medium (pH 6.8 phosphate buffer) maintained at 37 ± 0.5 °C and stirred at 50 rpm. Aliquots were collected periodically and replaced with fresh dissolution medium. Aliquots, after filtration through whatman filter paper
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were analysed spectrophotometrically at 432 nm for Curcumin content. The data was analysed using the software. 17-19

Stability Studies:
In order to evaluate the stability of the optimized SMEDDS the formulation was added into sealed glass vials and the vials were subjected to stability studies at 40°C ± 2°C/75% ± 5% RH for a period of three months. Samples were charged in stability chambers with humidity and temperature control. The samples were evaluated for clarity, phase separation, Drug content and in vitro drug release at predetermined intervals.20,21

RESULT AND DISCUSSION
Evaluation of SMEDDS:
Self emulsification, phase separation study and Globule Size Polydispersity index
The concentration of oil, surfactant and co-surfactant was optimized by preparing different batches of optimized formulation from each ratio was selected based on globule size, zeta potential, % transmittance and physical stability (centrifugation) characterization. Results were given in Table 5.

<table>
<thead>
<tr>
<th>Batch Code</th>
<th>Globules size(nm)</th>
<th>Drug content</th>
<th>PDI</th>
<th>Zeta potential</th>
<th>Phase Separation</th>
</tr>
</thead>
<tbody>
<tr>
<td>B1</td>
<td>86.19</td>
<td>97.27</td>
<td>0.1369</td>
<td>-23.66 mv</td>
<td>Not found</td>
</tr>
<tr>
<td>B2</td>
<td>58.73</td>
<td>97.3</td>
<td>0.1659</td>
<td>-14.51 mv</td>
<td>Not found</td>
</tr>
<tr>
<td>B3</td>
<td>35.9</td>
<td>95.51</td>
<td>0.0836</td>
<td>-0.77 mv</td>
<td>Not found</td>
</tr>
<tr>
<td>B4</td>
<td>74.7</td>
<td>97.08</td>
<td>0.0836</td>
<td>-0.78 mv</td>
<td>Not found</td>
</tr>
<tr>
<td>B5</td>
<td>41.65</td>
<td>97.58</td>
<td>0.344</td>
<td>-0.77 mv</td>
<td>Found</td>
</tr>
<tr>
<td>B6</td>
<td>45.01</td>
<td>97.96</td>
<td>0.344</td>
<td>-6.31 mv</td>
<td>Not found</td>
</tr>
<tr>
<td>B7</td>
<td>17.22</td>
<td>97.93</td>
<td>0.1596</td>
<td>-0.77 mv</td>
<td>Found</td>
</tr>
</tbody>
</table>

Drug content
B3 was showing drug content 99.51%. Drug content of the developed formulation was found near to 100% showing the chemical stability.

Centrifugation
As showed in figure 3 that no phase separation on centrifugation indicating physical stability of formulation.

Figure 3: Centrifugation study of optimized formulation In Vitro diffusion

Stability Studies
Samples of SMEDDS were charged on accelerated and long term stability conditions. Chemical and visual observations of samples were done. No significant change in the drug content in the formulations was observed over the period of 3 months at accelerated and long term stability conditions.

Solubility studies
Screening of excipients was done by determining the equilibrium solubility of curcumin in different oils, surfactants and co-surfactants. Vehicles should have good solubilizing capacity of drug substance, which is essential for composing SMEDDS.Curcumin had highest solubility in Pecoeol with comparison to other lipid vehicles. Curcumin had highest solubility in Labrasol as compare to other surfactant and co-surfactant. Furthermore Labrasol, Cremophor EL &Propylene glycol also showed very high solubility of Curcumin.For optimization of proper combination of surfactant / co-surfactant / oil several randomtrials were taken by mixing different ratios of surfactants & co-surfactants (Smix) with different oils. For the preliminary selection 0.5 ml Smix: oil ratios were prepared and then they were diluted with water by water titration method.Each trial was observed for clarity.From the different trails, the ratios which gave clear emulsion on dilution were selected forfurther study.
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Pseudoternary phase diagrams:
The phase diagrams were constructed at ratio of surfactant/co-surfactant 1:1, 2:1, 3:1, 4:1 (w/w). However, stability of self-emulsifying droplets from ratio of S/CoS = 1:1, S/CoS = 3:1 & S/CoS = 4:1 (w/w) was decreased because of precipitation after a few hours. So, ratio of S/CoS = 2:1 was chosen in formulation.

Figure: 5 Pseudo-Ternary phase diagram showing Microemulsion region for (a) Smix 1:1 (b) Smix 2:1 (c) Smix 3:1

Table: 1 Response of seven different formulations as per simplex lattice design

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Concentration (Actual value in ml for 1ml formulation)</th>
<th>Code value</th>
<th>Actual value (ml)</th>
<th>Code value</th>
<th>Actual value (ml)</th>
<th>Code value</th>
<th>Actual value (ml)</th>
<th>Code value</th>
<th>Code value</th>
<th>Code value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Surfactant (Labrasol)</td>
<td>X1</td>
<td></td>
<td>X2</td>
<td></td>
<td>X3</td>
<td></td>
<td>Y1</td>
<td>Y2</td>
<td>Y3</td>
</tr>
<tr>
<td></td>
<td>Co-surfactant (Cremophore EL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oils (Peceol:Ethyleolate) 1:1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B1</td>
<td>A</td>
<td>1</td>
<td>0.65</td>
<td>0</td>
<td>0.2</td>
<td>0</td>
<td>0.15</td>
<td>86.19</td>
<td>97.5</td>
<td>457.53</td>
</tr>
<tr>
<td>B2</td>
<td>B</td>
<td>0</td>
<td>0.5</td>
<td>1</td>
<td>0.35</td>
<td>0</td>
<td>0.15</td>
<td>58.73</td>
<td>96</td>
<td>59.72</td>
</tr>
<tr>
<td>B3</td>
<td>C</td>
<td>0</td>
<td>0.5</td>
<td>0</td>
<td>0.2</td>
<td>1</td>
<td>0.3</td>
<td>35.9</td>
<td>99.5</td>
<td>61.93</td>
</tr>
<tr>
<td>B4</td>
<td>AB</td>
<td>0.5</td>
<td>0.575</td>
<td>0.5</td>
<td>0.275</td>
<td>0</td>
<td>0.15</td>
<td>74.7</td>
<td>95.5</td>
<td>52.62</td>
</tr>
<tr>
<td>B5</td>
<td>AC</td>
<td>0.5</td>
<td>0.575</td>
<td>0</td>
<td>0.2</td>
<td>0.5</td>
<td>0.225</td>
<td>41.656</td>
<td>97</td>
<td>57.68</td>
</tr>
<tr>
<td>B6</td>
<td>BC</td>
<td>0</td>
<td>0.5</td>
<td>0.5</td>
<td>0.2</td>
<td>0.5</td>
<td>0.225</td>
<td>45.01</td>
<td>98</td>
<td>47.25</td>
</tr>
<tr>
<td>B7</td>
<td>ABC</td>
<td>0.33</td>
<td>0.55</td>
<td>0.33</td>
<td>0.25</td>
<td>0.33</td>
<td>0.2</td>
<td>47.22</td>
<td>96</td>
<td>60.22</td>
</tr>
</tbody>
</table>

\*X1= Concentration of Surfactant (Labrasol); X2= Concentration of Co-surfactant (Cremophore EL); X3= Concentration of Oil ratio (ethyl oleate: Peceol)
Y1= Mean globule size; Y2= %Transparency; Y3= Drug diffuse in 10 min

Formulation Optimization

The equation for simplex lattice model is described as follows:

\[ R = \beta_a A + \beta_b B + \beta_c C + \beta_ab AB + \beta_ac AC + \beta_bc BC + \beta_{abc} ABC \ldots (1) \]

Where \( R \) is the dependent variable and \( \beta_i \) is the estimated coefficient for the factor(A/B/C). The major effects (A, B, and C) represent average results of changing one factor at a time from its low to high value, the interactions AB, BC, AC, and ABC6. According to simplex lattice design and the selected concentration ranges of Surfactant, Co-surfactant & Oil, seven different formulations of SMEDDS containing curcumin were constructed. The results of their Mean droplet size, % transparency, and amount of drug diffused in 10 minute were given in Table.

Mix order special cubic model was selected for optimization study. With the help of software Design Expert 8.0.5, the fitted results are shown in Equations (2), (3) and (4):

\[ R1=35.850A + 50.30B + 0.025C+54.48AB-63.650BC+22.85AC -187.510ABC... (2) \]

\[ R2 = 95.50A + 99.50B + 95.80C + 3.28AB -1.00AC + 1.40BC + 28.56ABC... (3) \]

\[ R3 = 67.39A +93.72B+68.81C + 29.70AB - 17.80AC + 0.58BC - 173.22ABC... (4) \]

Equations (2), (3) and (4) can be used to calculate the predicted values for other formulations in the design space. The chosen concentrations of surfactant, cosurfactant and oil were reintroduced into above Equations (2), (3) and (4). The results of ANOVA suggested that \( F \) as well as \( P \) values are significant.

A ternary contour plot can be used to examine relations between four dimensions where three of those dimensions represent components of a mixture (i.e., the relations between them is constrained such that values of three variables add up to the same constant).
One typical application of this graph is when the measured responses from an experiment depends on relative proportions of three components (Surfactant, Co-surfactant and oil) that are varied in order to determine an optimal combination of those components. Graphics of Mean globule size, % Transparency and Amount of curcumin diffused in 10 minutes were constructed in form of Ternary contour plots (Design Expert 8.0.5 software), shown in figure 6 and optimized formulation was chosen by suggested trials by special cubic model.

**Figure: 6 Ternary contour plot for Curcumin SMEEDDS**

- a: Mean globule size
- b: % Transparency
- c: Amount of Curcumin diffused in 10 minutes from Curcumin SMEEDDS

The overlay plot for Variables showing optimized batch B-3.

Batch B3 was selected as optimized batch in order to obtain high % transparency and higher % diffusion and smallest possible Mean globule size. The appropriate ratio of components for optimized formulation B3 was, oil (15%), surfactant (35%), co-surfactant (50%).

**Validation of applied design by checkpoint.**

One extra design checkpoint was taken and the checkpoint batch was prepared. The checkpoint batch was evaluated for all the three dependent variables. The practically obtained responses of the checkpoint batch were compared with the calculated responses from the simplex equations.

**Table: 2 Checkpoint prediction**

<table>
<thead>
<tr>
<th>Batch code</th>
<th>Variable level</th>
<th>Coded value</th>
<th>Actual value in %</th>
</tr>
</thead>
<tbody>
<tr>
<td>CP</td>
<td>A</td>
<td>0.342</td>
<td>0.391</td>
</tr>
<tr>
<td>R1</td>
<td>Mean globule size</td>
<td>= 43.90 (0.342) + 22.95 (0.391) + 41.00 (0.267) - 4.50 (0.342) - 3.50 (0.391) - 16.20 (0.267) - 188.76 (0.342) - 35.87 (0.391) + 28.56 (0.267)</td>
<td></td>
</tr>
<tr>
<td>R2</td>
<td>% Transparency</td>
<td>= 95.50 (0.342) + 99.50 (0.391) + 95.80 (0.267) + 3.28 (0.342) - 1.00 (0.342) + 1.40 (0.391) + 28.56 (0.267)</td>
<td></td>
</tr>
<tr>
<td>R3</td>
<td>% Amount of drug diffused in 10 min</td>
<td>= 67.39 (0.342) + 93.72 (0.391) + 68.81 (0.267) + 29.70 (0.342) - 17.80 (0.391)</td>
<td></td>
</tr>
</tbody>
</table>

Practically obtained responses are closer to the practical response. Closeness of the equation justifies the validation of design.

**CONCLUSION**

Optimized SMEEDDS formulation (B3) had no effect of accelerated condition like centrifugation and freeze-thaw cycle. In vitro diffusion studies revealed that release of curcumin from SMEEDDS was faster. Thus our studies confirmed that SMEEDDS can be used as a possible alternative to conventional oral formulation of curcumin. Results further conclude that SMEEDDS can be explored as a potential drug carrier for dissolution enhancement of curcumin and other insoluble drugs.

**REFERENCES**


