Formulation Design of Self-Microemulsifying Drug Delivery Systems for Improved Oral Bioavailability of Celecoxib

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Celecoxib is a hydrophobic and highly permeable drug belonging to class II of biopharmaceutics classification system. Low aqueous solubility of celecoxib leads to high variability in absorption after oral administration. Cohesiveness, low bulk density and compressibility, and poor flow properties of celecoxib impart complications in its processing into solid dosage forms. To improve the solubility and bioavailability and to get faster onset of action of celecoxib, the self-microemulsifying drug delivery system (SMEDDS) was developed. Composition of SMEDDS was optimized using simplex lattice mixture design. Dissolution efficiency, t95%, absorbance of diluted SMEDDS formulation and solubility of celecoxib in diluted formulation were chosen as response variables. The SMEDDS formulation optimized via mixture design consisted of 49.5% PEG-8 caprylic/capric glycerides, 40.5% mixture of Tween20 and Propylene glycol monocaprylic ester (3:1) and 10% celecoxib, which showed significantly higher rate and extent of absorption than conventional capsule. The relative bioavailability of the SMEDDS formulation to the conventional capsule was 132%. The present study demonstrated the suitability of mixture design to optimize the compositions for SMEDDS. The developed SMEDDS formulations have the potential to minimize the variability in absorption and to provide rapid onset of action of celecoxib.

Key words self- microemulsifying system; mixture design; bioavailability; celecoxib; microemulsion

Celecoxib (4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]-benzenesulphonamide, is a specific cyclo-oxygenase-2 (COX-2) inhibitor with no inhibition of cyclo-oxygenase-1 at therapeutic doses. It is being used successfully for the treatment of rheumatoid arthritis, osteoarthritis, acute pain, familial adenomatous polyposis and primary dysmenorrhea.1,2) Celecoxib also demonstrated significant chemopreventive activity in colon carcinogenesis, ultraviolet B radiation (UVB) induced skin cancer and breast cancer.3—5) Celecoxib is weakly acidic (pKa is 11.1) and hydrophobic (Log P is 3.5) and its low aqueous solubility (3—7 μg/ml) contributes to high variability in absorption after oral administration.6)

The molecule exists in three polymorphic forms and its solid-state interconversion between the forms at ordinary temperatures has not been observed. It is isolated as agglomerates of long needle-shaped crystals, which exhibit cohesiveness, low bulk density and compressibility, and poor flow properties that impart complications in its processing into solid dosage forms.7) According to biopharmaceutical classification system, celecoxib is classified as a low solubility and high permeability drug.8) Therefore, the particle size of celecoxib influences the content uniformity, dissolution and bioavailability of the product. The t∞% of celecoxib is about three hours after oral administration. Rapid onset of action is necessary to provide fast pain relief in the treatment of acute pain. Therefore, it is necessary to enhance the aqueous solubility and dissolution rate of celecoxib to obtain faster onset of action, to minimize the variability in absorption and improve its overall oral bioavailability. This can be achieved by formulating the drug in lipid-based systems.

Among the lipid-based systems, self-microemulsifying drug delivery system (SMEDDS) is a promising technology to improve the rate and extent of the absorption of poorly water-soluble drugs.9—15) The clinical usefulness of the SMEDDS is evident from the commercially available formulations containing cyclosporin A, ritonavir and Saquinavir.16, 17) SMEDDS are comprised of mixture of drug, oil, surfactant(s) and/or co-solvents which form fine oil in water microemulsions upon dilution with aqueous medium or in vivo administration. SMEDDS enhances the bioavailability of poorly water-soluble drugs through solubilization in the excipient matrix and interface and dispersion in the gastrointestinal tract. Relatively small size of the dispersed oil droplets in nanometer range and very high surfac e area to volume ratio are advantages of the microemulsion. These characteristics result in faster drug release from microemulsion in a reproducible manner, which can be designed further to make the release characteristics independent of the gastrointestinal physiology and the fed/fasted state of the patient.5,18—20)

In this study, we have developed an optimized formulation using a self-microemulsifying system in order to improve the solubility and to get faster onset of action of celecoxib. Composition of SMEDDS has been optimized using mixture design. Dissolution efficiency, t95%, absorbance of diluted SMEDDS formulation and solubility of celecoxib in diluted formulation has been chosen as response variables. Bioavailability of optimized SMEDDS formulation has been compared with conventional capsule.

MATERIALS AND METHODS

Materials Tween80 (Polyoxyethylene sorbitan monoleate, HLB=15) and Tween20 (Polyoxyethylene sorbitan monolaurate, HLB=16.7) were purchased from Sigma, U.S.A. Captex 200(C10/C16 diesters of propylene glycol, DPG), Capmul PG-8 (Propylene glycol monocaprylic ester, MPG), Acconon MC-8 (PEG-8 caprylic/capric glycerides, CCG) were gift samples from Abitec Corporation, U.S.A. Captex 200 (C8/C10 diesters of propylene glycol, HLB=16.7) were purchased from Sigma, U.S.A. Captex 200 (C8/C10 diesters of propylene glycol, HLB=16.7) were purchased from Sigma, U.S.A.

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Sodium dodecyl sulphate (SDS) were of analytical grade purchased from E-Merck, India. Celecoxib was a gift from Zyduz Cadila Pvt. Ltd., India. Acetonitrile and methanol were of HPLC grade products purchased from SRL Chemicals, India. Water, doubly distilled in an all glass still, was used in all experiments. All other chemicals used were of analytical grade. All chemicals were used as received.

**Screening of Oils and Surfactants** The solubility study was used to identify the suitable oil and surfactant that possess good solubilizing capacity for celecoxib. Solubility of celecoxib in vegetable oils (soya bean oil, olive oil, and castor oil), isopropyl myristate, DPG, MPG and surfactants (Tween80, Tween20 and CCG) was determined by adding excess amount of drug and continuously stirring for at least 72 h at 30 °C. The mixtures were centrifuged (2500×g, 30 min) and supernatant was filtered through 0.45 μm membrane filter. Drug concentration in the filtrate was determined using an HPLC system (Shimadzu, Japan) consisting of a pump, a UV/VIS detector, a NCI 900 network chromatography interface and an instrument software (TotalChrom). Drug concentration in the filtrate was determined spectrophotometrically at 253 nm.

Effect of surfactant to oil ratio on the solubility of celecoxib was determined by adding excess amount of drug to each composition of different weight ratios of surfactant to oil ranging from 4:1 to 1:4. The samples were continuously stirred for 72 h at 30 °C. The samples were centrifuged (2500×g, 30 min) and the supernatant was filtered through 0.45 μm membrane filter. Drug concentration in the filtrate was determined by HPLC after appropriate dilution with acetonitrile.

**Construction of Phase Diagram** Pseudo ternary phase diagram was constructed by titration of homogenous liquid mixtures of oil, surfactant and secondary surfactant with water at room temperature. Stock solutions of surfactant and oil at different mass ratios (2:1 and 3:1) were prepared. These stock solutions were mixed with different amounts of CCG in stoppered test tubes and stirred until clear. Water phase was added drop-by-drop using a micro syringe to each oily mixture until the onset of turbidity or phase separation. During the titration, samples were stirred vigorously for a sufficient length of time for homogenization and the end product was visually monitored against a dark background by illuminating the samples with white light. In order to establish the microemulsion region borders, mixture of water and CCG was titrated with oil and surfactant mixture in the same manner.

Formation spontaneity of microemulsion was evaluated by the addition of known amount of water at once to the known amount of oil, surfactant and secondary surfactant with controlled stirring. The ease of formation of clear microemulsion was taken as the criteria of spontaneity.

**Optimization of SMEDDS Formulation** Very few reports appeared in literature about optimization of self (micro or nano) emulsifying drug delivery systems using experimental design. In this study, we have followed a simplex lattice mixture design to optimize the composition of SMEDDS formulation for an in vivo study. SMEDDS was prepared as follows: MPG, the oil and Tween20, the surfactant were weighed in a stoppered flask in the ratio of 1:3, vortexed vigorously and then stored overnight at room temperature. A predetermined weighed amount of mixture of MPG and Tween20 are stirred together with CCG to form a homogeneous mixture.

**Spectroscopic Characterization of Optical Clarity** The optical clarity of aqueous dispersions of SMEDDS formulation was measured spectrophotoscopically. Compositions were prepared according to the design and diluted to 25 times with double distilled water. The absorbance of each solution was measured at 400 nm, using double distilled water as standard.

**Solubility Determination** Excess amount of celecoxib was added to the aqueous dispersions of SMEDDS formulation used in the above study. The mixture was vortexed and allowed to stand for 24 h to get equilibration. The supernatant was filtered through 0.45 μm membrane filter and analyzed spectrophotometrically at 253 nm after appropriate dilution with methanol.

**Dissolution Studies** Dissolution studies were performed according to the USP XXII paddle method. SEMDDS containing 50 mg of celecoxib was filled in hard gelatin capsules and introduced into 500 ml of a dissolution medium consisting of 0.25% SDS in double distilled water and maintained at 37 °C. The Revolution speed of the paddle was kept constant at 100 rpm. The aliquot of 5 ml was withdrawn at 0, 3, 6, 9, 15, 30, 45, 60 and 90 min, and filtered through 0.45 μm membrane filters. The concentration of celecoxib was determined spectrophotometrically at 253 nm.

**In Vivo Study** Six healthy male volunteers (3 in each group) between the ages of 27 to 33 years were administered a single dose of celecoxib with 200 ml of water. Subjects were fasted for at least 8 h before their scheduled treatment regimen. Group A volunteers received hard gelatin capsule containing 200 mg of celecoxib (Celact®, Celecoxib 200 mg) while group B volunteers were administered SMEDDS containing 200 mg celecoxib filled in hard gelatin capsules. Blood samples (5 ml) were collected before dosing and at 0.5, 1, 1.5, 2, 3, 5, 8, 12 and 24 h after dosing into EDTA containing tubes. Plasma was obtained by centrifugation of blood samples for 20 min at approximately 3000×g at 10 °C. The plasma samples were stored at −20 °C until analysis. Local ethics committee of Jadavpur University, Kolkata, had approved the study protocol. All volunteers gave their written informed consent prior to participating in the study. The concentration of celecoxib was determined using an HPLC system (PerkinElmer, U.S.A.) consisting of a Series 200 Pump and UV/VIS detector, a NCI 900 network chromatography interface and an instrument software (TotalChrom).

**Plasma Celecoxib Assay** Human plasma (1 ml) containing celecoxib and 100 μl internal standard (Rofecoxib) was vortexed for approximately 1 min. The proteins were precipitated with 1 ml of saturated sodium chloride and 1 ml of acetonitrile. The samples were extracted with 6 ml of dichloromethane: chloroform (50:50, v/v) for 10 min and then centrifuged at 2000×g for 20 min. The organic layer was transferred to a clean tube and evaporated under a stream of nitrogen at 40 °C. The residue was dissolved in...
150 µl of mobile phase by vortex mixing and centrifuged. An aliquot (20 µl) of the sample extract was injected into a C-8 Finepak column (5 µm, 25 cm×4.6 mm; Jasco Corporation, Japan). The mobile phase, acetonitrile/methanol/0.05 M potassium biphosphate buffer pH 3 (50 : 10 : 40, v/v), was run at a flow rate of 1.0 ml/min. The column eluent was monitored at a wavelength of 249 nm. The peak area of celecoxib was determined and compared to the standard curve in order to determine the plasma concentration of celecoxib. Calibration curves were prepared with spiked plasma over the range of 25 to 1500 ng/ml. The correlation coefficient \((r^2)\) for the calibration curve was 0.957.

**Pharmacokinetic Calculation** The plasma celecoxib concentration-time curves after single oral dose administration was analyzed by non-compartmental analysis using Winnonlin 4.1 software. The \(AUC_{0-24}\) is the area under the plasma concentration–time curve from time 0 to time of the last observed concentration after an oral dose (24 h) was calculated using the linear trapezoidal rule. The \(AUC_{0-\infty}\) is the late area under the plasma concentration–time curve from time 0 to infinity, calculated by dividing the last observed plasma concentration by \(λ_d\), where \(λ_d\) denotes the first order rate constant of the terminal phase.

**Statistical Analysis** The statistical significance of the difference between mean values was assessed by use of Student's \(t\)-test. Statistical probability \((p)\) values less than 0.05 were considered significantly different.

RESULTS AND DISCUSSION

**Screening of Oils and Surfactants** Development of microemulsion systems for poorly water soluble drugs is critical. Drug loading per formulation is a very critical design factor, which is dependent on the drug solubility in various formulation components. The volume of the formulation should be as minimized as possible to deliver the therapeutic dose of the drug in an encapsulated form. Components selected for the formulation should have the ability to solubilize the drug in high level to obtain a concentrate form of microemulsions.

Non-ionic surfactants are used in this study since they are known to be less affected by pH and changes in ionic strength.\(^{23}\) Results of solubility studies on the celecoxib in various oils and surfactants are presented in Table 1. MPG and DPG provided higher solubility than other oils. Among the non-ionic surfactants studied, Tween 80 showed highest solubility of celecoxib (315.4 mg/ml). DPG was very difficult to be solubilized into the non-ionic micelles using a single non-ionic surfactant.\(^{24}\) Certain mixture of non-ionic surfactants has been reported to enhance the solubilization of water in water-in-oil microemulsion.\(^{25}\) The areas of one phase microemulsion zones produced by the mixture of non-ionic surfactants are the function of surfactant composition.\(^{26}\) Attempt has been made to enhance the solubilization of DPG using the mixture of non-ionic surfactants. The low irritant non-ionic surfactant, CCG was recently used in the formulation of topical microemulsions while use of CCG in oral formulations is limited.\(^{27-30}\) CCG also showed good solubility of drug (300.9 mg/ml). Hence, SMEDDS was developed using combination of Tween80, Tween20 and CCG.

<table>
<thead>
<tr>
<th>Oil/Surfactant</th>
<th>Solubility (mg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soybean oil</td>
<td>3.57±0.44</td>
</tr>
<tr>
<td>Castor oil</td>
<td>4.36±1.23</td>
</tr>
<tr>
<td>Olive oil</td>
<td>3.12±0.42</td>
</tr>
<tr>
<td>IPM</td>
<td>6.04±0.72</td>
</tr>
<tr>
<td>Captex 810</td>
<td>6.55±0.71</td>
</tr>
<tr>
<td>DPG</td>
<td>14.7±0.85</td>
</tr>
<tr>
<td>Captex-355</td>
<td>14.25±0.74</td>
</tr>
<tr>
<td>MPG</td>
<td>52±1.09</td>
</tr>
<tr>
<td>CCG</td>
<td>300.9±1.35</td>
</tr>
<tr>
<td>Tween80</td>
<td>315.4±2.07</td>
</tr>
<tr>
<td>Tween20</td>
<td>303.1±1.93</td>
</tr>
</tbody>
</table>

Table 1. Solubility of Celecoxib in Different Oils and Surfactants at 25 °C (Mean±S.D., n=3)

Smedds was developed using combination of Tween80, Tween20 and CCG (Tween80 to DPG and Tween20 to PMG) was determined and presented in Figs. 1 and 2. The solubility of celecoxib in mixture of Tween80 and DPG increased from 93.6 to 298.3 mg/ml as the ratio of Tween80 to DPG increased from 1 : 4 to 4 : 1. On the other hand the solubility of celecoxib in mixture of Tween20 and MPG increased from 347.2 mg/ml as the ratio of Tween20 to MPG increased from 1 : 4 to 3 : 1, but further increase in Tween20 resulted in decrease...
in celecoxib solubility. These results are in line with other reported observations. Increasing concentration of surfactant increases the viscosity of the mixture. The surfactant to oil ratio of 3 : 1 and 2 : 1 was selected to construct the phase diagrams.

**Pseudo-Ternary Phase Diagram**  
Pseudo-ternary phase diagrams were constructed to identify self micro-emulsifying regions and to select suitable concentrations of oil, surfactant and secondary surfactant for the formulation of SMEDDS. Mixtures of Tween80 and DPG were prepared in the ratio of 2 : 1 and 3 : 1. The prepared ratios were mixed with CCG and titrated with water to construct the phase diagram. Similar approach was adopted for the mixtures of Tween20 and MPG, and these diagrams are presented in Figs. 3 and 4. The monophasic zones produced by the present systems were high at 3 : 1 ratio of surfactant to oil. The homogeneous mixture consisting of Tween20, MPG and CCG produced larger region of monophasic zone than mixture containing Tween 80, DPG and CCG. The results indicate that the one phase microemulsion area in both the mixed systems is the sum of the contributions of all the components, which is in line with the report of Ajith and Rakshit. The former system produced low viscosity and more formation spontaneity than the latter in all the studied ratios. Increasing concentration of CCG in the mixture has increased the spontaneity of the self-emulsification process. DPG was successfully solubilized in the presence of combination of non-ionic surfactants. Mixtures composed of Tween80, DPG and CCG were able to solubilize higher amounts of the drug than the mixtures of Tween20, MPG and CCG. Hence, the latter was selected for further optimization, since it possessed low viscosity, high self emulsification region and better spontaneity.

**Optimization of SMEDDS Formulation**  
Two-component simplex lattice mixture design was used to optimize the composition of SMEDDS for oral delivery of celecoxib. Mixture experiments are defined as an experiment where the response is assumed to depend only on the relative proportions of the components present in the mixture and not on the amount of the mixture itself. This is what is expected for the SMEDDS. In this design, 5 design points and 3 check points were generated using Design Expert™ software. We have followed two methods to optimize the formulations. In the first method, the response variables were absorbance (1 part of SMEDDS diluted to 25 parts with double distilled water) and solubility of celecoxib in the above-formed microemulsions. In the second method, design contained 10% of celecoxib keeping OSM (mixture of Tween20 and MPG in the ratio of 3 : 1) and CCG in the same ratio as in formulations of first method, and the responses were t₈₅% and dissolution efficiency. Based on the pseudo-ternary diagram the concentrations of the components were selected. Generated design points with response values are summarized in Tables 2 and 3. Based on the F value, lack of fit and other statistics, model of best fit was chosen by the program.

SMEDDS was diluted with water to know whether these systems could form microemulsions with the external phase of the system without phase separation or not. The optical clarity of aqueous dispersion can be assessed visually in qualitative manner. In order to assess the optical clarity quantitatively, UV–visible spectrophotometer was used to measure the amount of light of given wavelength transmitted by the solution. Higher transmittance should be obtained with optically clear solutions, since cloudier solutions will scatter more of the incident radiation, resulting in lower transmittance. Aqueous dispersions with small absorbance are opti-
Dissolution studies were performed for SMEDDS containing 10% of celecoxib according to design points (Table 3). The release of celecoxib from these formulations was evaluated in 0.25% SDS solution and these profiles are presented in Fig. 5. The release profiles were characterized by $t_{85\%}$ and dissolution efficiency (DE). Pharmacopoeias very frequently use $t_{85\%}$ parameter as an acceptance limit of the dissolution test. US-FDA guidance for immediate release product suggested that 85% ($t_{85\%}$) of labeled amount of drug should be released within 30 min of study. Therefore, $t_{85\%}$ and DE were kept as response variables. DE is a measure of the dissolution curve up to a certain time $t$, expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time. DE of SMEDDS was calculated by the following equation:

$$DE = \int_0^{t_{85\%}} \frac{dy}{y_{85\%} \times t}$$

where, $y$ is cumulative percentage of drug released. DE of SMEDDS varied from 78 to 92% while $t_{85\%}$ of these formulations varied from 6.96 to 27.6 min. Data of DE and $t_{85\%}$ from the SMEDDS formulations were found to show best fit to linear model. The prediction equations for the DE and $t_{85\%}$ are given as follows

$$DE = 0.704542 (OSM) + 1.228986 (CCG)$$
$$t_{85\%} = 0.508375 (OSM) - 0.26496 (CCG)$$

Table 2. Simplex Lattice Mixture Design Points with Response Variables (Method 1)

<table>
<thead>
<tr>
<th>Design points</th>
<th>OSM (%)</th>
<th>CCG (%)</th>
<th>Absorbance</th>
<th>Solubility (mg/ml)</th>
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<tbody>
<tr>
<td>1</td>
<td>70</td>
<td>30</td>
<td>0.376</td>
<td>0.79</td>
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<tr>
<td>2</td>
<td>57.5</td>
<td>42.5</td>
<td>0.029</td>
<td>0.84</td>
</tr>
<tr>
<td>3</td>
<td>45</td>
<td>55</td>
<td>0.022</td>
<td>0.91</td>
</tr>
<tr>
<td>4</td>
<td>63.75</td>
<td>36.25</td>
<td>0.162</td>
<td>0.82</td>
</tr>
<tr>
<td>5</td>
<td>51.25</td>
<td>48.75</td>
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<td>0.88</td>
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<tr>
<td>6</td>
<td>45</td>
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<td>0.024</td>
<td>0.9</td>
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<tr>
<td>7</td>
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<td>0.77</td>
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<tr>
<td>8</td>
<td>57.5</td>
<td>42.5</td>
<td>0.027</td>
<td>0.87</td>
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Table 3. Simplex Lattice Mixture Design Points with Response Variables (Method 2)*

<table>
<thead>
<tr>
<th>Design points</th>
<th>Formulation</th>
<th>OSM (%)</th>
<th>CCG (%)</th>
<th>$t_{85%}$ (min)</th>
<th>Dissolution efficiency (%)</th>
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<tbody>
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<td>1</td>
<td>1</td>
<td>63</td>
<td>27</td>
<td>27.6</td>
<td>78.25</td>
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<tr>
<td>2</td>
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<td>51.75</td>
<td>38.25</td>
<td>13.94</td>
<td>82.6</td>
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<tr>
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<tr>
<td>4</td>
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<td>57.375</td>
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<td>7.87</td>
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<td>38.25</td>
<td>11.37</td>
<td>83.53</td>
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*Contains 10% celecoxib. OSM: mixture of Tween20 and MPG in the ratio of 3 : 1; CCG: PEG-8 caprylic/capric glycerides.
tions. As expected, formulations with lower absorbance had the highest DE. The response variables of the optimized formulation were experimentally determined in triplicate and the results are shown in Table 4.

Highest release rate observed with formulation 3 was due to contribution of the composition which consists of higher amount of secondary surfactant and lower amount of oil. Further, quicker self-emulsification nature of this composition also plays a role in faster and complete drug release.

In Vivo Study  Optimized SMEDDS consisted of 49.5% CCG, 40.5% mixture of Tween20 and MPG (3 : 1) and 10% celecoxib were selected for in vivo evaluation in fasted human male volunteers after consideration of the solubility of celecoxib, self-microemulsification process and dissolution efficiency. The plasma profiles of celecoxib in human volunteers following oral administration of the conventional capsule and SMEDDS formulation were compared. The mean plasma concentration versus time profiles of celecoxib is presented in Fig. 6. The corresponding mean pharmacokinetics parameters of these formulations are summarized in Table 5. Relative bioavailability of SMEDDS formulation to the conventional capsule was 132%. The present study demonstrated the suitability of mixture design to optimize the compositions for SMEDDS. The developed SMEDDS formulations have the potential to minimize the compositions for SMEDDS. The developed SMEDDS formulation optimized via mixture design consisted of 49.5% CCG, 40.5% mixture of Tween20 and MPG (3 : 1) and 10% celecoxib, which showed significantly higher rate and extent of absorption than conventional capsule. The relative bioavailability of the SMEDDS formulation to the conventional capsule was 132%. The developed SMEDDS consisted of less amount of oil making them less prone to gastric emptying delays and resulting in faster absorption. The preliminary optimization helped us to improve bioavailability by 132%; other different systems are currently under investigation for further enhancement of bioavailability.

CONCLUSION

The SMEDDS formulation optimized via mixture design consisted of 49.5% CCG, 40.5% mixture of Tween20 and MPG (3 : 1) and 10% celecoxib, which showed significantly higher rate and extent of absorption than conventional capsule. The relative bioavailability of the SMEDDS formulation to the conventional capsule was 132%. The developed SMEDDS formulations have the potential to minimize the variability in absorption and to provide rapid onset of action of celecoxib. The developed formulation is expected to be a welcome addition to clinical arsenal for prompt and efficacious acute pain and inflammation management.

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