Pharmacophore 2013, Vol. 4 (4), 120-133 USA CODEN: PHARM7 ISSN 2229-5402

Pharmacophore

(An International Research Journal)

Available online at http://www.pharmacophorejournal.com/

Original Research Paper

FORMULATION DEVELOPMENT OF SELF NANOEMULSIFYING DRUG DELIVERY SYSTEM (SNEDDS) OF CELECOXIB FOR IMPROVEMENT OF ORAL BIOAVAILABILITY

Gurjeet Kaur, Pankaj Chandel and **S.L. Harikumar***

Department of Pharmaceutics, Rayat and Bahra Institute of Pharmacy, Sahauran, Distt. Mohali, Punjab, India-140104

ABSTRACT

Celecoxib is a hydrophobic and highly permeable drug which belongs to class II of biopharmaceutics classification system (BCS). Low aqueous solubility of celecoxib leads to high variability in absorption after oral administration. The present study was carried out for the formulation development of celecoxib loaded self nanoemulsifying drug delivery system (SNEDDS) with the aim of enhancement of oral bioavailability. The SNEDDS formulation was optimized using pseudo-ternary phase diagram composed of capryol 90, cremophor RH 40 and propylene glycol. Six formulations (F1, F2, F3, F4, F5 and F6) were developed with varying concentration of oil, surfactant and co-surfactant by sonication technique. The self nano-emulsifying drug delivery system of celecoxib was characterized for content uniformity, particle size, poly dispersity index, viscosity determination and robustness of dilution, drug loading efficiency and shape of globules, thermodynamic stability and self emulsification efficiency. In vitro dissolution and in vitro diffusion studies were also carried out to get final optimized formulation. The optimized celecoxib SNEDDS (F6) found to contain surfactant content less than 30% and yielded nanoemulsion of mean droplet size 169.4nm, which was not affected by the pH of dilution media. The zeta potential of the optimized SNEDDS (F6) found to be -32.9 mV. The drug loading efficiency of the formulation F6 was high at 98.98%. The developed celecoxib loaded SNEDDS formulation exhibited a complete *in vitro* drug release in 1hr as compared with the plain drug. Thus, the self nanoemulsifying drug delivery system (SNEDDS) using celecoxib as model drug found to achieve effective therapeutic concentration and intended to provide relief from pain associated with inflammation by single dose administration as compared to conventional tablets as well as prevent the cardiac risks due to lower dose size.

Keywords: BCS, Celecoxib, Pseudo-ternary phase diagram, Dissolution rate, SNEDDS.

INTRODUCTION

The oral route constitutes as the most familiar means of drug administration, mainly because it is the most natural and convenient for the patient. Oral route of administration has been received more attention in the pharmaceutical field, because of the more flexibility in the designing of dosage form than drug delivery design for other routes. The oral drug delivery depends on various factors such as type of delivery system, the disease being treated and the patient, the length of the therapy and the properties of the drug.[1] The major limitation of oral route of drug administration that drugs taken orally for systemic effects have variable absorption rates and variable

serum concentrations which may be unpredictable. This has led to the development of sustained release and controlled release systems. The novel drug delivery for oral route has become a major research area in the field of pharmaceutical drug delivery along with the discovery of new chemical entities that are potent enough and may also have very short biological half lives. Most of the novel drug delivery systems (NDDS) relay on diffusion, dissolution or combination of both mechanisms, to release the drug to the gastro intestinal tract (GIT). Furthermore, a majority of the new chemical entities being generated through drug discovery programs also exhibit poor water solubility (BCS class II and IV). The problems associated with such drugs include poor oral bioavailability, erratic absorption profile, high intra- and inter-subject variability and lack of dose proportionality.[2] The potential of nanoemulsion /SNEDDS in improving oral bioavailability of atorvastatin and ezetimibe has been established[3]; the increase in the drug bioavailability need not translate into increases in the pharmacodynamic effects of these drugs.[4] Such aspects should be carefully considered while planning investigations on the SNEDDS.

Self-nanoemulsifying drug delivery systems (SNEDDS) are anhydrous homogenous liquid mixtures consisting of oil, surfactant, drug and coemulsifier or solubilizer, which spontaneously form oil-in-water nanoemulsion of approximately 200 nm or less in size upon dilution with water under gentle stirring.[5,6] Celecoxib is a hydrophobic (log P=3.5) and weakly acidic (pKa= 11.1) drug. It is a white crystalline powder which is practically insoluble in water which contributes to high variability in absorption after oral administration.[7] It is usually administered as one or two daily oral doses, for an overall dosage of 100-200mg twice a day. It is used to decrease growths found in the intestines (colon polyps) of persons with a family history of this condition. The physicochemical properties, drug solubilization capacity and physiological fate considerably govern the selection of the SNEDDS components. The composition of the SNEDDS can be optimized with the help of phase diagrams, whereas statistical experimental design can be used to further optimize SNEDDS. Preliminary studies indicate that the encapsulation of celecoxib in lipophilic vesicular structure (SNEDDS) may be expected to enhance the absorption of the drug from the GIT following oral ingestion and prolong the existence of the drug in systemic circulation due to the slow release of the encapsulated drug.

SNEDDS can improve oral bioavailability of celecoxib by several mechanisms. The conversion of liquid SNEDDS to solid oral dosage form or solid SNEDDS has to be achieved. Solid SNEDDS can offer better patient compliance and minimize problems associated with capsules filled with liquid SNEDDS. The self nanoemulsifying system can also be employed to fabricate extended release delivery systems for poorly soluble drugs.[8] Therefore, the major objective of the present research is to provide and maintain adequate concentration of drug at the site of action which is otherwise is due to presence of physiological barriers along the way of drug passage leads to poor absorption of drugs with small fractions of the administered dose that is reaching the circulation, through a novel formulation, self nanoemulsifying drug delivery system.

MATERIALS AND METHODS

MATERIALS

Celecoxib was provided by Symbiosis Pharmaceuticals Pvt. Ltd. Sirmour (H.P.). Capryol 90 and Labrafil M 2125 CS was obtained from Gattefosse SAS, France as gift sample. Cremophor RH 40 was obtained as gift sample from Signet Chemical Corporation Pvt. Ltd. Cellophane membrane was purchased from Himedia Ltd., Mumbai, India. Other materials used were of analytical grade, and provided by the institution.

METHODS

Selection of SNEDDS Components

Oil (Solubility Studies)

The solubility of celecoxib in various oils (sesame oil, soyabean oil, castor oil, olive oil, isopropyl myristate, labrafil M 2125 CS and capryol 90) was

determined by visual observation. Accurately measured 10 ml of each solvent taken in thoroughly cleaned & dried test tubes. The known amount of celecoxib added subsequently to each test tube till saturation. The mixtures were vortexed and heated as required and, the amount of drug that was suspended in various solvents was determined.[9] The solubility of celecoxib in various buffers (1.2, 6.8, 7.4), surfactants (tween20, tween 80 and Cr RH40) and co surfactants (methanol, ethanol and propylene glycol) was measured by shake flask method.[3] An excess amount of celecoxib was added into 5 ml of each solvent and the mixtures were kept in capped bottles and vortexed to facilitate solubilization if required. Capped bottles were stirred in water bath at 37^0C for 72 hrs. Each mixture was centrifuged at 15,000 rpm for 10 min. and filtered. Samples were then diluted with methanol (100 times) and drug concentration was determined by UV-VIS double beam spectrophotometer in each sample at 254nm using methanol as a blank.

Surfactant (Emulsification Study)

Surfactant was selected on the basis of percent transparency and ease of emulsification. Various surfactants (Cremophor® RH 40, span 20, span 80, tween 20 and tween 80) were selected to determine the emulsification ability of the selected oil phase. 300 mg of each surfactant was added to 300 mg of selected oil in different test tubes. The mixtures were heated gently for homogenization. Then, 50 mg from each mixture was diluted with 50 ml distilled water in corked conical flask. Number of flask inversions required to obtain a homogeneous emulsion were determined to know the ease of emulsification. Emulsions were then allowed to stand for 2 h and the optical clarity of aqueous dispersion was assessed visually in qualitative manner and UV-VIS spectrophotometer was used to measure the amount of light of given wavelength transmitted by the solution. The emulsions were further observed for any turbidity or phase separation.[9,10]

Cosurfactant (emulsification study)

Cosurfactant was also selected on the basis of % transparency and ease of emulsification. Labrafil M 2125 CS, PEG 200, PEG 400 and PG were screened for SNEDDS formulation. 100 mg of cosurfactant was mixed with 200 mg of selected surfactant and 300 mg of selected oil and was evaluated similarly as was described for surfactant selection.[9]

Fourier Transform Infrared Spectroscopy

The infrared absorption spectra of celecoxib and mixture of celecoxib with polymer in ratio 1:1 were obtained in a potassium bromide disk to determine any interaction between the drug and the excipients. The spectra were recorded on an IR-1600 Perkin Elmer infrared spectrophotometer.

Optimization of SNEDDS

Construction of ternary phase diagram

Ternary phase diagram was constructed by dilution method as described by Kommuru *et al*. (2001). The mixtures of oil, surfactant and cosurfactant were prepared in which concentration of oil varied from 30 to 70% w/w, surfactant concentration also varied from 30 to 70% w/w and the concentration of cosurfactant varied from 0 to 30% w/w. But, the total concentration of the mixture containing oil, surfactant and cosurfactant was always added to 100%. In the experiment, first mixture consisted of 30% of oil (capryol 90), 70% of surfactant (Cremophor RH 40) and 0% of cosurfactant (propylene glycol). Subsequently, in further mixtures, oil concentration was kept constant, cosurfactant concentration was increased by 5% for each composition and the surfactant concentration was adjusted to obtain a total of 100%. 50 mg of each of the compositions was then diluted to 50 ml with double distilled water to evaluate the composition for nanoemulsion formation by determining the % transparency, globule size and poly dispersity index of the resulting dispersion by dynamic light scattering (DLS) with zeta sizer.[11, 12]

Dispersions having particle size less than or equal to 200 nm were considered desirable for the construction of ternary diagram as well as for drug loading. The corresponding compositions of the dispersions with desirable particle size were

plotted to obtain the area of nanoemulsion (NE) formation for the respective system in which nanoemulsion with desired globule size was obtained.[13]

Formulation of SNEDDS

SNEDDS formulations of celecoxib were prepared by varying the concentrations of Capryol 90 as the oil, Cremophor RH 40 as surfactant and Propylene glycol as the cosurfactant. The amount of oil, surfactant and co-surfactant to be taken was decided on the basis of nanoemulsification region in the ternary phase diagram. Celecoxib was accurately weighed into screw-capped glass vials and dissolved in capryol 90. The mixture was warmed in a water bath at 37^0 C. Cremophor RH 40 and propylene glycol were added to the mixture and stirred for 10 minutes using a magnetic bar. The formulations were further sonicated at 45^0 C for 15 minutes. Six formulations with different concentrations of surfactant, co-surfactant and oil, each containing celecoxib at a final loading of 60 mg were filled in hard gelatin capsules. Filled capsules were stored at room temperature until used in subsequent studies. Composition of various SNEDDS formulations of celecoxib elaborated in Table 4.

Evaluation of SNEDDS

Drug content uniformity

5 capsules from each batch of formulations (F1 to F6) were emptied into 50 ml volumetric flask containing 30 ml methanol. The capsule shells were thoroughly rinsed with 10 ml methanol. The flasks were sonicated for 15 min, and then final volumes were made up to 50 ml with methanol. The samples were filtered and the solutions were assayed for celecoxib by UV-VIS spectrophotometer at 254 nm.[12]

Droplet size and zeta potential

SNEDDS formulation was determined by diluting 50mg of SNEDDS to 50ml with distilled water. About 2ml of the sample was placed in a cubid and analyzed by diffraction light scattering with zeta sizer Nano-ZS (Malvern Instrument Ltd.) at 25 ^{0}C and a scattering angle of 173^0.

Poly dispersity index

Uniformity of globule size in SNEDDS formulation was also analyzed by diffraction light scattering with zeta sizer Nano-ZS (Malvern Instrument Ltd.) at 25^0C and a scattering angle of 173^0.

Viscosity determination

The viscosity of the celecoxib SNEDDS formulation was determined by zeta sizer to conform whether the system was w/o or o/w type emulsion.

Robustness to dilution

The effect of dilution was evaluated by diluting 50mg of SNEDDS to 50ml with various dissolution media viz. water, phosphate buffers (pH 1.2, 6.8 & 7.4). The diluted formulations were stored and observed after 12h for any signs of phase separation or drug precipitation.[13]

Drug loading efficiency

The percentage of drug entrapped in globules was determined by mixing 50 mg of formulation with methanol to make up the volume up to 50 ml on magnetic stirrer for 8h. Supernatant was filtered and analyzed spectrophotometrically at 254 nm.[14]

$$\text{Drug loading efficiency} = \frac{\text{Initial drug load} - \text{Amount of drug in filtrate}}{\text{Initial drug load}} \times 100$$

Morphological study

The SNEDDS globules were observed by transmission electron microscope. Sample was visualized by drying it on carbon-coated grid and stained negatively with aqueous solution of phosphotungstic acid. After drying the phosphotungstic acid, the sample was observed under TEM.[15]

Thermodynamic stability study

Thermodynamic stability studies were performed for celecoxib SNEDDS formulation in three steps:

- *Heating-cooling cycle:* Celecoxib SNEDDS filled in hard gelatin capsules were stored alternatively at 4^0C and at 45^0C. The capsules were stored for 48 h at each temperature and repeated to complete six cycles. The capsules that withstand the heating cooling cycle were subjected to centrifugation test.

- *Centrifugation test:* the selected capsules were centrifuged (REMI LJ 01, Mumbai) at 5000 rpm for 30minutes and observed for any sign of phase separation, creaming or cracking. The capsules showed maximum stability were selected for freeze-thaw cycles.
- *Freeze-thaw cycles:* Capsules passed the centrifugation test were exposed at -21^{0}C and 21^{0}C. Capsules were stored at each temperature for not less than 24h and the capsules found to withstand the harsh conditions of the temperature changes were selected for further evaluation studies.[16]

Dispersibility test

The efficiency of self-emulsification of celecoxib SNEDDS was assessed by using a standard USP 24 dissolution apparatus 2. Stable SNEDDS formulation containing celecoxib equivalent to 60 mg was filled into hard gelatin capsule and put into 900ml of PBS 7.4 at 37^{0}C $\pm$ 1^{0}C. The paddle was rotated at speed of 50 rpm to provide gentle agitation. The *in vitro* performance of the formulations i.e. time taken for capsule shell to burst and release its content to dissolution media was visually assessed and graded as A, B, C, D or E as per dispersibility test grading system.[17]

In vitro dissolution study

Dissolution study of formulated SNEDDS filled in hard gelatin capsules was carried out using USP 24 rotating basket apparatus (Tablet Dissolution Rate Test Apparatus, Spruce Enterprise) at 37$\pm$ 0.5^{0}C and rotating speed of 100 rpm in 900 ml of PBS 7.4. 5 ml sample was withdrawn after 10 min. Subsequently, dissolution media was replaced with equal volume to maintain the sink condition. The sample was assayed for celecoxib using UV-VIS spectrophotometer at 254 nm. To study the effect of pH on SNEDDS formulation, dissolution study was carried out with phosphate buffer (pH 1.2 & 6.8) as dissolution media. Dissolution study of capsules containing pure drug was also done in order to compare the percent release of the drug from the capsules containing pure drug with that of the SNEDDS formulation.[18]

In vitro diffusion study

In vitro diffusion behaviour of celecoxib from the SNEDDS formulation was investigated using cellophane membrane (Molecular weight cut of 12000-14000, HI Media Ltd, Mumbai, India.). The vertical type of Franz Diffusion cell was designed, fabricated and validated prior to diffusion study. One gram of SNEDDS was placed on 9.98 cm^2 area of the surface of cellophane membrane tied to the lower end of donor compartment. The volume of the receptor fluid was kept 37.5 ml. The temperature of the receptor fluid maintained at 37^{0}C and stirred continuously at 100 rpm on a magnetic stirrer. Aliquots of 1.0 ml were withdrawn and analyzed for the drug content after suitable dilutions by spectrophotometric method. The volume of fluid was replaced with the same volume of fresh buffer after each sampling. The cumulative amount diffused across the cellophane membrane was calculated and plotted against time.[18,19]

RESULTS AND DISCUSSION

SELECTION OF SNEDDS COMPONENTS

Screening of Oils

Solubility studies were carried out to identify a suitable oil for the formulation of celecoxib SNEDDS. Various oily phases including vegetable oils as well as mineral oils were screened for the solubility determinations from which Capryol® 90 was found to solubilize the maximum amount of celecoxib (340 mg/ml). Solubility test of celecoxib in various solvents listed in Table 1.

Screening of Surfactants

Results inferred that Capryol® 90 as an oily phase exhibited the maximum emulsification efficiency with Cremophor® RH 40 possessing percent transmittance 109$\pm$0.2% with 5$\pm$1 flask inversions for the formation of homogenous emulsion. While, Capryol®90 with other surfactants showed poor emulsification properties because higher number of flask inversions required for the formation of homogenous emulsion (Table 2). These results suggested the use of Cremophor®

RH 40 as a surfactant with capryol 90 as an oily phase for further studies.

Screening of Co-surfactants

Table 3 represents the emulsification efficiency (number of flask inversions) and percent transmittance of various co-surfactants. Among which propylene glycol exhibited highest emulsification efficiency with 10±2 flask inversion and maximum percent transmittance 98.6±1%. Results inferred the importance of addition of co-surfactant to the dispersions containing surfactant as those dispersions exhibited instantaneous emulsion formation.

Drug- Excipient Interaction

Fourier transform infrared spectroscopy (FTIR) is the most commonly used technique for the identification of the drug-excipients interaction. The presence of interaction is detected by the disappearance of important functional group of the drug (Moffat, 1986). The spectra were recorded between 4000 cm^{-1} and 670 cm^{-1} under the same operational conditions. The spectra of celecoxib and celecoxib & Cremophor RH 40 are shown in Figure1. The peak obtained from FTIR spectra of celecoxib represented in Figure 1a, at 1149 cm^{-1} and that was obtained by mixing Cremophor RH 40 with celecoxib in 1:1 ratio showing the peak at 1155cm^{-1}. The absorbance spectrum of celecoxib and Cremophor RH 40 showed several characteristic peaks. The spectrum of drug and polymer mixture had the feature of each of the components and did not change the infra red spectrum of celecoxib. Thus, there was found no chemical interaction in the binary system which indicated that the molecular structure of celecoxib remained completely intact.

OPTIMIZATION OF SNEDDS

Construction of Pseudo-Ternary Phase Diagram

Formation of stable and efficient SNEDDS is determined by the ratio of surfactant to co-surfactant. Hence, the ternary diagram was constructed at the ratio of surfactant to co-surfactant 9:5, 4:3, 5:1, 7:5, 3:2, 1:1, 7:1, 3:1 and 5:3 (w/w). The increased concentration of Cr RH 40 results in more turbid region while increased concentration of propylene glycol were found to expand the self nanoemulsifying region. However, the self nanoemulsifying region found to be maximum at 3:2 ratio of surfactant to co-surfactant with no drug precipitation observed after 12 h. On the other hand, higher concentration of cosurfactant responsible for the instability of the system due to high intrinsic aqueous solubility that lead to increased droplet size hence resulted in expansion of interfacial film. Therefore, 5:3 ratio of surfactant to co-surfactant was selected as optimal. On the basis of above results, three component SNEDDS formulations (F1, F2, F3, F4, F5 and F6) were established. Ternary phase diagram is given in Figure 2.

FORMULATION OF SNEDDS

Six formulations of celecoxib SNEDDS were formulated by selecting the composition of oil, surfactant and co-surfactant from the zeta sizer results of the combinations without drug (E, H, M, N, O and Q) on the basis of particle size and poly dispersity index. The combinations possessing particle size less than 200 nm and poly dispersity index below 0.3 were considered suitable for drug loading. Compositions of various SNEDDS formulation of celecoxib are represented in Table 4.

EVALUATION OF SNEDDS

Drug Content Uniformity

The percent drug content of F1, F2, F3, F4, F5, & F6 formulations presented in Table 9 and was observed that the % drug content of all the formulations lie between 85% & 115% of average content. Hence, all the formulations prepared in this study complied within the limits indicating the uniform distribution of drug throughout in the formulations of SNEDDS.[18]

Droplet Size and Poly Dispersity Index

Globule size of celecoxib SNEDDS formulation is found to be decreased with reduction in oil content. When S_{mix} : Oil ratio was 7:3, the droplet size formed was smaller in comparison with 3:2, 1:1, 2:3 and 3:7 ratio of S_{mix} : Oil. However, at 4:3 ratios of surfactant and co-surfactant, smaller droplets were formed than at 5:1, 3:2 and 5:3 ratio of S_{mix}. Among the six formulations, F6 gave the

smallest particle size (169.4 nm) at 2:3 ratio of S_{mix} : Oil. The poly dispersity index below 0.3 indicates good uniformity in the droplet size distribution after dilution with water (Pouton, 1985; Gershanik & Benita, 2000 and Kang *et al*., 2004) that was obtained only for F6 (0.283). The droplet size and poly dispersity index of SNEDDS formulation is shown in Table 9. F6 was found to confirm the selection criteria of SNEDDS. Therefore, only F6 formulation of celecoxib SNEDDS was selected for further evaluation studies. Zeta sizer reports of celecoxib SNEDDS F6 for particle size and poly dispersity index are shown in Figure 3.

Zeta Potential

The another property that was assessed for increased absorption of SNEDDS is the charge of the oil droplets which is usually found to be negative due to the presence of free fatty acids. Moreover, Cremophor RH40 is a nonionic surfactant which is a mixture results from the reaction of glycerol tri-hydroxystearate with about 40 to 50 moles of ethylene oxide. F6 SNEDDS with smallest particle size having the zeta potential -32.9 mV. Hence, the optimized SNEDDS (F6) would not exhibit threshold agglomeration as the nanoemulsion was stabilized by a greater zeta potential (negative) and steric stabilization effect. The droplet size and poly dispersity index of six formulations & zeta potential of F6 are represented in Table 9. The zeta sizer report for zeta potential of F6 SNEDDS of celecoxib is shown in Figure 4.

Viscosity Determination

Viscosity determination is important to determine the type of emulsion. The viscosity of the SNEDDS formulations was evaluated by zeta sizer. If the system has low viscosity then it is o/w type of the system and if there is high viscosity then it is w/o type of the system.[20, 21] As the viscosity of the system was found to be very low indicating o/w type of emulsion.

Robustness to Dilution

Distilled water, acidic buffer (pH 1.2), phosphate buffer (pH 6.8 &7.4) were used as dispersion medium in the current investigation. The diluted SNEDDS formulation of celecoxib (F6) with 250 ml of each dispersion media showed no visible signs of phase separation or drug precipitation after storage for 12 h at 37 $\pm$ 0.5^{0}C.

Drug Encapsulation Efficiency

Drug loading capacity of optimized formulation was high at 98.98% which usually depends on the amount of oil in the formulation. Greater the concentration of oil more will be the drug loading in the SNEDDS formulation.

Globule Visualization by Transmission Electron Microscopy (TEM)

TEM of the selected formulation (F6) SNEDDS was performed for morphological examination and confirmation of particle-size analysis. TEM image of nanoformulation after dilution in distilled water (1:1000) is depicted in Figure 5. The figure revealed spherical nanoemulsion globules less than 200 nm in size, confirming the results obtained by the Malvern Zeta sizer. Spherical, discrete, and non aggregated globules in SNEDDS formulation inferred the system stability. A thicker darker wall of nanoemulsion globules can be seen in the SNEDDS image which may be ascribed to surface accumulation of celecoxib. SNEDDS developed showed drug molecules loaded inside the globules, as revealed in higher magnification images of drug-loaded SNEDDS.

Thermodynamic Stability Studies

Thermodynamic stability studies performed for F6 SNEDDS appeared to pass all the three stages. There was not found any effect of heating-cooling cycle, centrifugation as well as freeze-thaw cycle on the physical stability of F6 SNEDDS. F6 SNEDDS formulation of celecoxib was able to withstand the harsh environment of temperature changes and showed no sign of drug precipitation, phase separation and shell brittleness or deformation.[26]

Dispersibility Test

The F6 SNEDDS was self-emulsified in just 30 seconds and was clear in appearance. The results inferred that F6 SNEDDS was graded as Grade A self-emulsified system which was in accordance with the standard grading system [22]. Therefore, F6

formulation will remain as nano-emulsion when dispersed in GIT. Hence, it is acceptable for oral use.

In vitro Dissolution Study

Dissolution studies were performed for conventional capsule and SNEDDS containing 60 mg of celecoxib. The release of drug from these formulations was evaluated in phosphate buffer saline 7.4 and these profiles are presented in Figure 6. As, the droplet size of F6 was found to be very small, having increased surface area, thus, allowing more dissolution and drug release. Hence, the drug release from F6 was found to be highest at 100.01% after 60 min at pH 7.4.

The release profile of celecoxib from conventional capsule was found to be very low at 13.03% and 14.5% after 45 min & 60 min respectively, which was due to the poor aqueous solubility of the drug To determine the effect of pH, the dissolution studies were performed for the optimized SNEDDS in phosphate buffers of different pH (1.2, 6.8 & 7.4) and these profiles are presented in Table 11. The release profile of SNEDDS at pH 1.2 was found to be lowest at 96.09% after 60 min and highest at 100.04% after 60 min in PBS 7.4. As was observed from release profile for F6 SNEDDS, the increase was much smaller from aqueous solution at acidic pH to basic pH. Thus, pH change had negligible effect on the drug release from the SNEDDS formulation. This observation can be explained by the fact that celecoxib has no ionizable group and thus, its solubility and dissolution is pH independent.[23] The release of a drug occurs due to its partitioning to aqueous media during droplet transport and disintegration along the GIT. Thus, the effective delivery of celecoxib from SNEDDS primarily governed by small particle size and polarity of the resulting oil droplets, that permits a faster rate of drug release into the aqueous phase.[24]

In vitro Diffusion Study

In vitro diffusion studies were performed for conventional capsule and SNEDDS containing celecoxib. Maximum amount of percent drug diffused from the optimized formulation F6 was 99.60% after 75 min which was less as compared to conventional capsule, 14.0% as shown in Figure 7. On comparing the data obtained from drug release profile with that of drug diffusion profile, it was found that there was not any significant difference in the release behavior. Greater drug diffusion was observed during diffusion study across cellophane membrane from F6 as compared to conventional capsule but lesser than that was obtained from dissolution study that was due to presence of membrane. The data of the *in-vitro* drug dissolution study suggests that the SNEDDS formulation, F6 followed Higuchi's diffusion model while the drug release from conventional capsule followed the first order release kinetics.

CONCLUSION

In the present study, SNEDDS of celecoxib was successfully developed and assessed for its in vitro performance. The nanosize of these formulations is responsible for facilitating enhancement of drug dissolution and absorption, owing to the large surface area. The lipidic nature of these systems allows delivery of drugs to the lymphatic system. The method employed in the investigation for screening of SNEDDS excipients helped in understanding the emulsification efficiency of various surfactants for selected oily phase. It also helped in rapid screening of large pool of co-surfactants available for the peroral delivery. Moreover, the smaller particle size and shorter emulsification time could promote absorption of drug.

From these results, SNEDDS might provide a useful dosage form for oral water-insoluble drug. It can be concluded that SNEDDS formed from capryol 90, Cremophor RH 40 and propylene glycol is a promising approach to improve the solubility, dissolution rate and bioavailability of celecoxib because of the simple manufacturing process, low production costs and the possibility of manufacturing at industrial scale. The present study may serve as a prototype approach for the formulation development of other hydrophobic drugs as self nanoemulsifying drug delivery system.

ACKNOWLEGDEMENT

Authors are thankful to Symbiosys Pharmaceuticals Pvt. Ltd. for kindly donating gift sample of celecoxib. Thanks also to Signet Chemical Corporation Pvt. Ltd. and to Gattefosse SAS, France for kindly providing Cremophor RH 40 and capryol 90 & Labrafil M 2125 CS respectively.

Table 1: Solubility of celecoxib in various oils

Oily phase	Solubility mean ± SD (mg/ml)
Sesame oil	160 ± 5
Labrafil M 2125 CS	50 ± 3
Capryol 90	340 ± 5
Soyabean oil	3 ± 1
Castor oil	4 ± 1
Olive oil	3 ± 1
Isopropyl myristate	6 ± 1

where n=3

Table 2: Surfactant emulsification study

Surfactant	No. of flask inversions mean ± SD	% Transparency mean ± SD
Cremophor RH 40	5 ± 1	109 ± 0.2
Span 20	23 ± 1	58.3 ± 0.6
Span 80	25 ± 4	54 ± 0.13
Tween 20	12 ± 2	101.67 ± 0.21
Tween 80	8 ± 5	98.7 ± 0.05

where n=3

Table 3: Co-surfactant emulsification study

Co-surfactant	No. of flask inversions mean ± SD	% Transparency mean ± SD
PEG 200	60 ± 3	50.4 ± 4
PEG 400	58 ± 2	63.9 ± 3
Propylene glycol	10 ± 2	98.6 ± 1
Labrafil M 2125 CS	66 ± 4	43.4 ± 3

where n=3

Table 4: Compositions of various SNEDDS formulations of celecoxib

Formulation	F1	F2	F3	F4	F5	F6
Celecoxib (mg)	60	60	60	60	60	60
Capryol 90 (mg)	240	240	300	300	360	360
Cr-RH 40 (mg)	300	210	180	150	210	150
PG (mg)	60	150	120	150	30	90

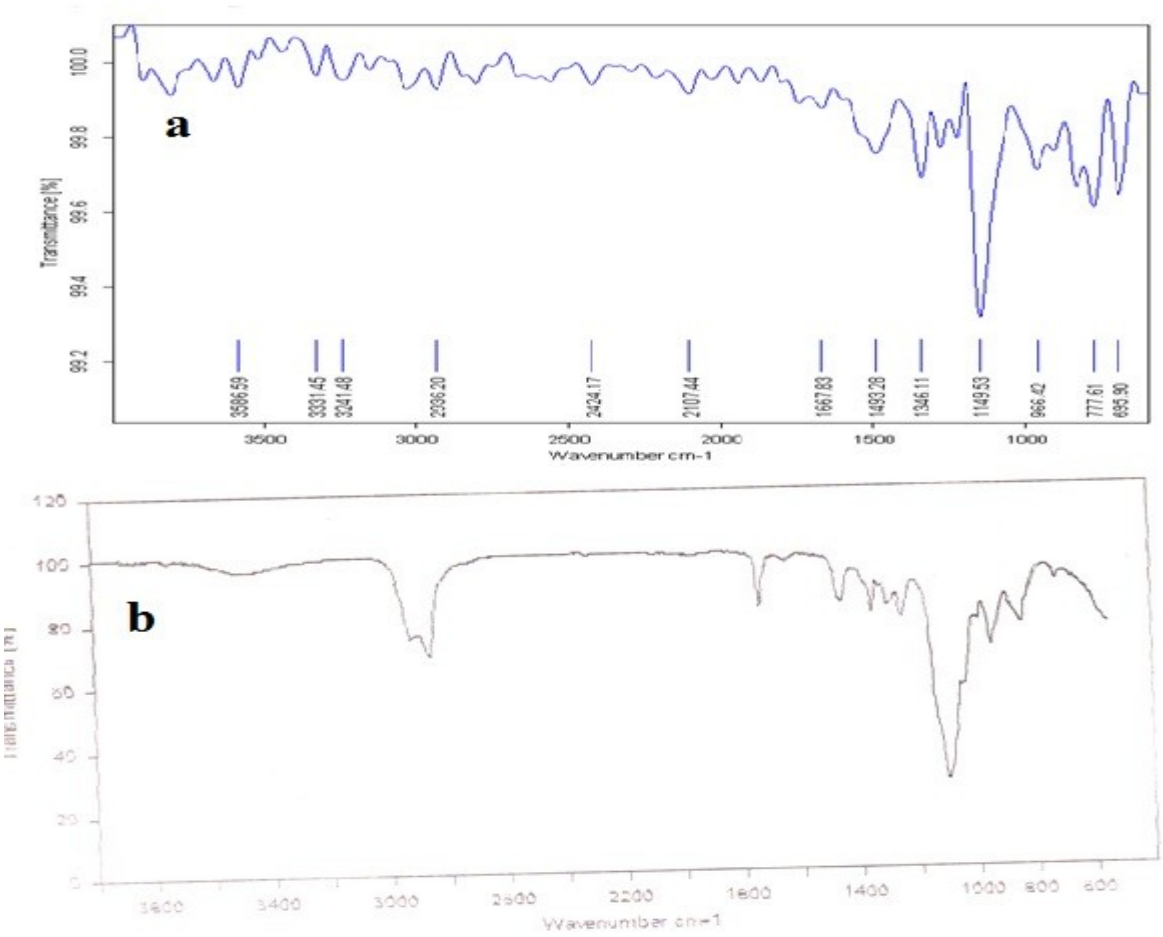

Figure 1: a. FTIR spectra of celecoxib b. FTIR spectra of celecoxib and Cremophor RH 40

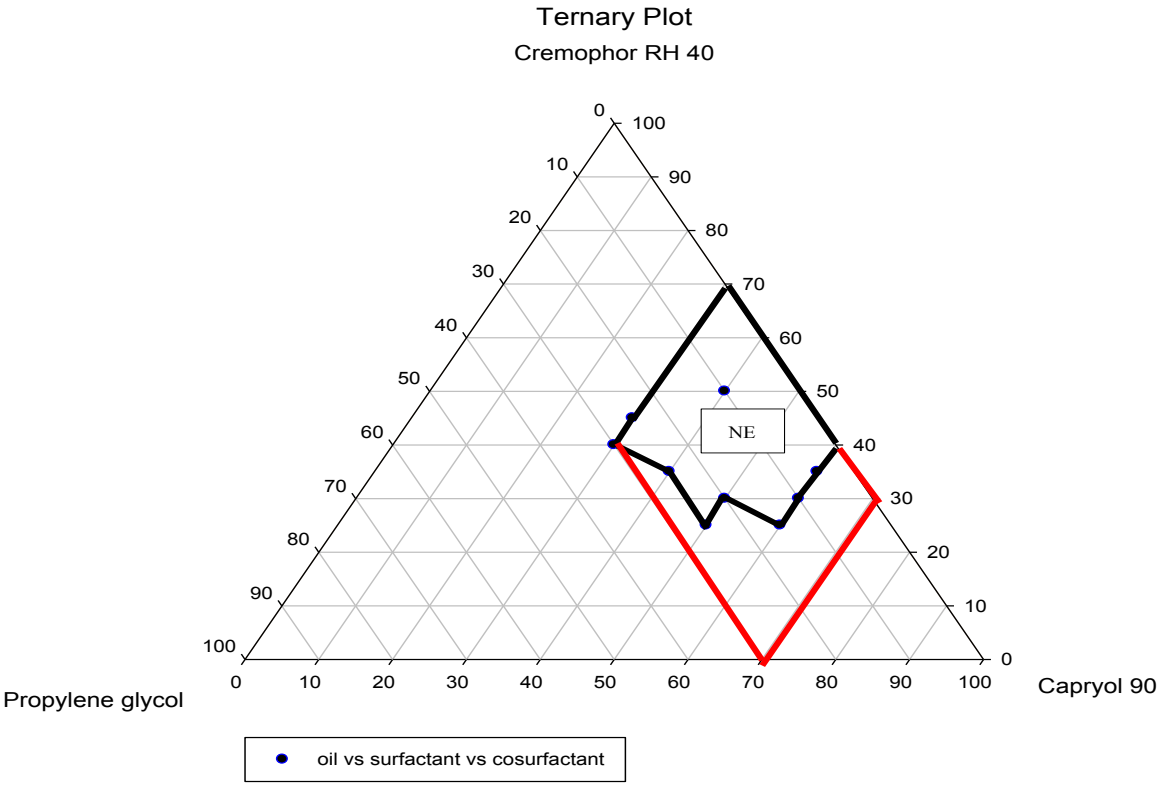

Figure 2: Pseudo-ternary phase diagram of capryol 90, Cr RH 40 and PG

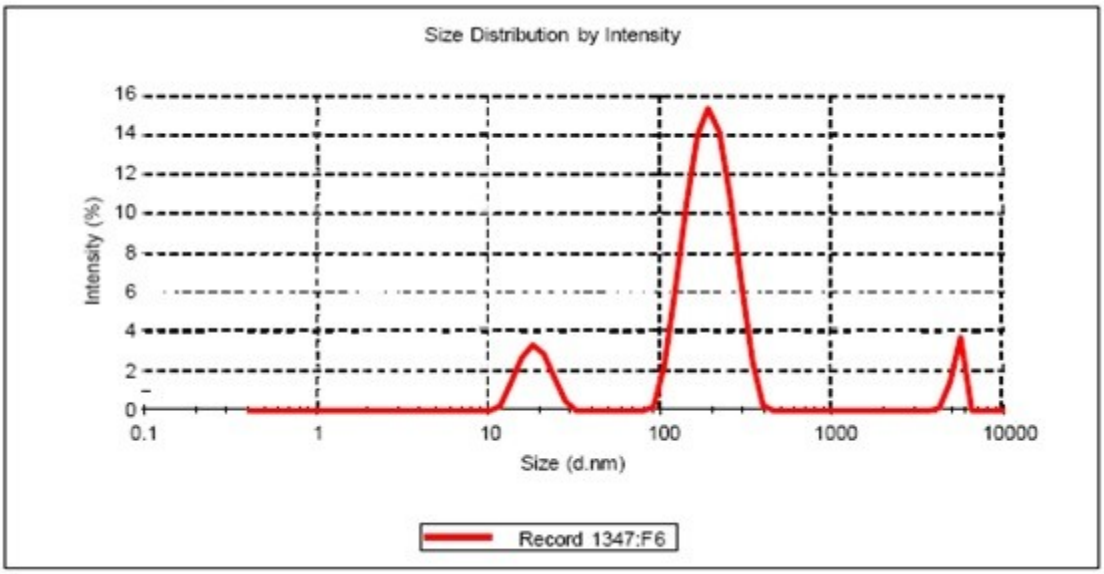

Figure 3: Zeta sizer report of celecoxib SNEDDS F6

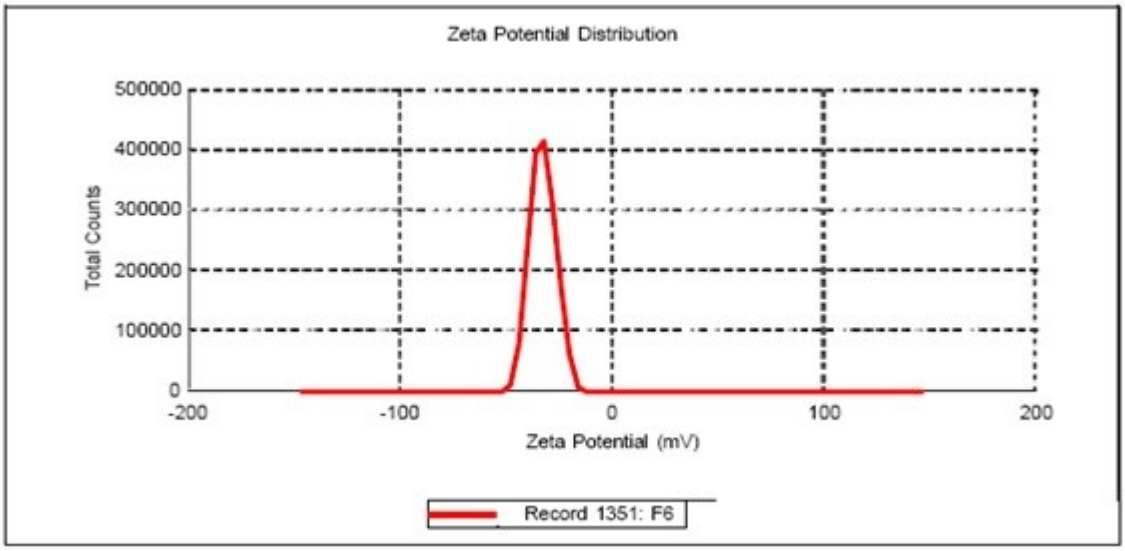

Figure 4: Zeta potential report of celecoxib SNEDDS F6

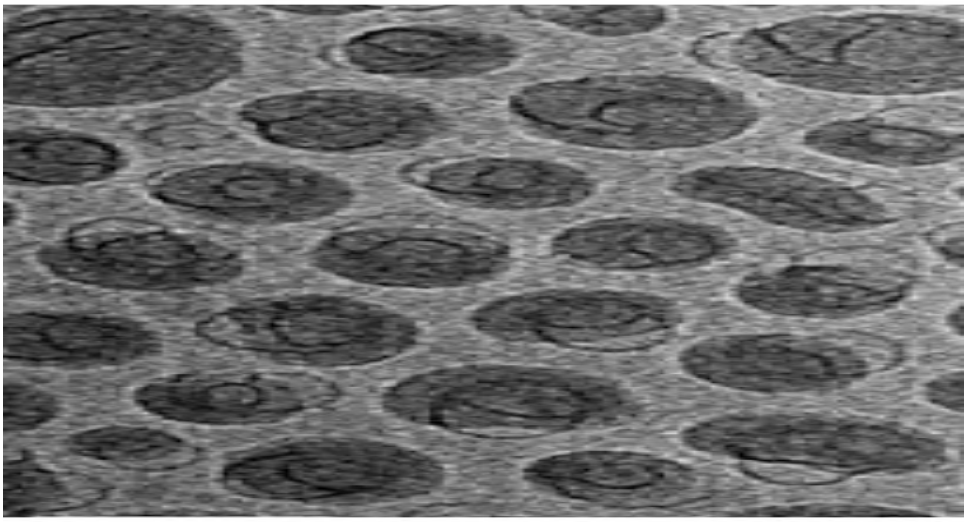

Figure 5: Photomicrograph of TEM of F6 SNEDDS

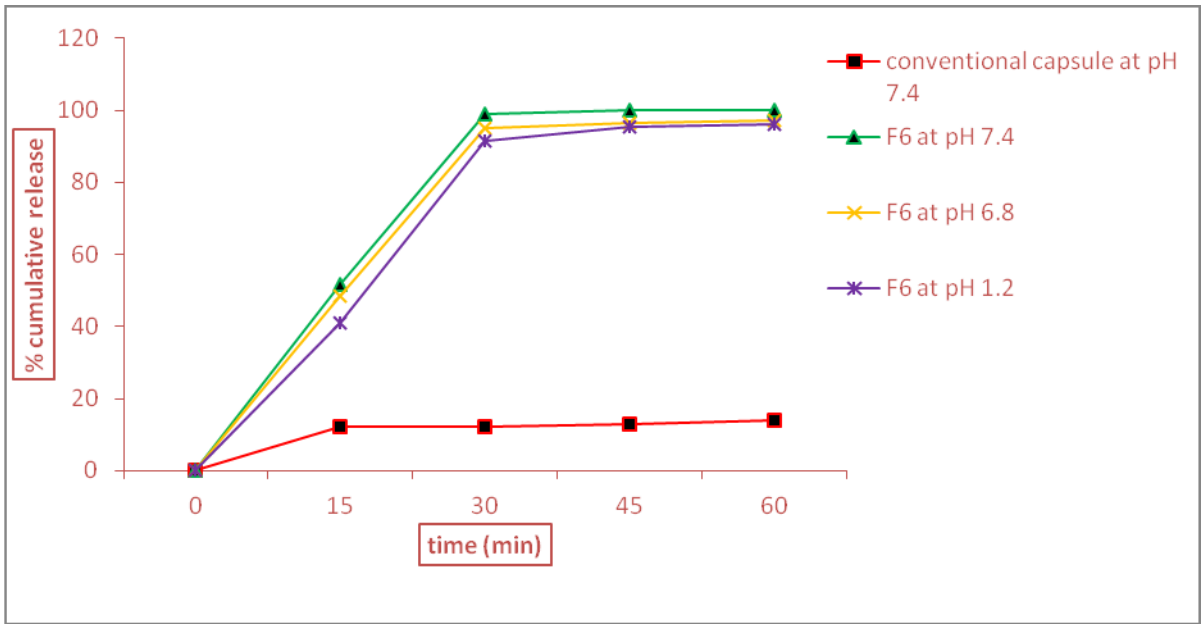

Figure 6: *In vitro* drug release profile of celecoxib from conventional capsule and SNEDDS at different pH

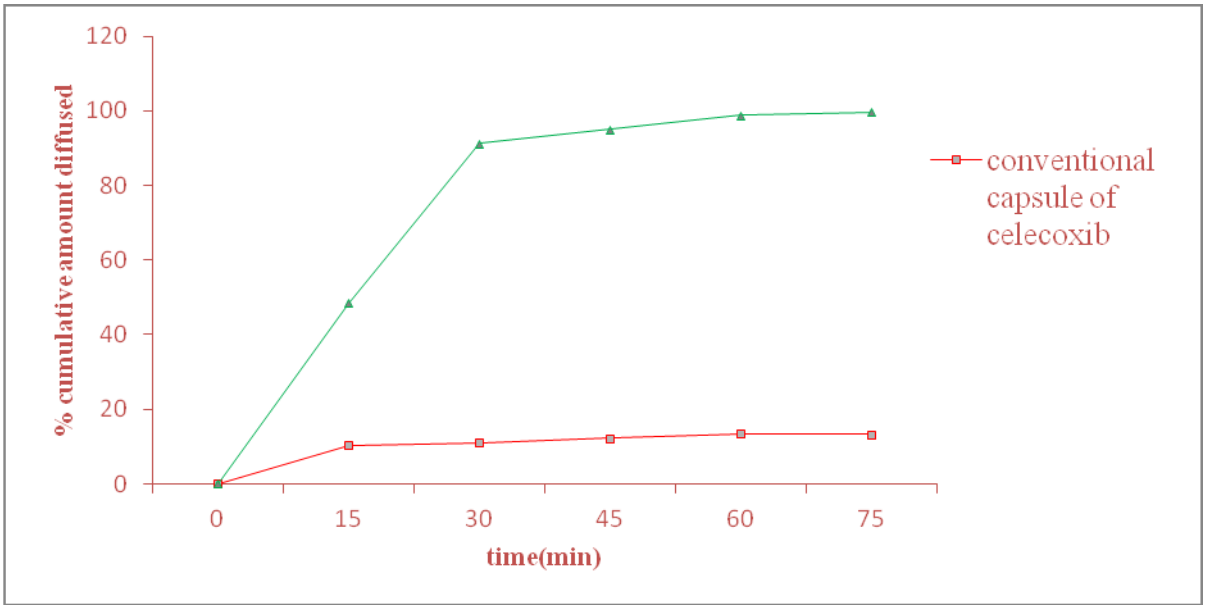

Figure 7: *In vitro* drug diffusion profile of celecoxib from conventional capsule and SNEDDS at pH 7.4

REFERENCES

1. Patil, P; Vandana, P and Paradkar, P (2007), "Formulation of selfemulsifying drug delivery system for oral delivery of simvastatin: In vitro and in vivo evaluation," ***Acta pharma.***, 57, 111.
2. Gershanik, T and Benita, S (2000), "Self-dispersing lipid formulations for improving oral absorption of lipophilic drugs," ***Eur J Pharm Biopharm.***, 50, 179.
3. Date, AA and Nagarsenker, MS (2007), "Novel Delivery Systems of Atorvastatin should be Evaluated for Pharmacodynamics Instead of Pharmacokinetics," ***J. Pharm. Pharmacol***., 59, 1583.
4. Bali, V; Ali, M and Ali, J (2010), "Study of Surfactant Combinations and Development of a Novel Nanoemulsion for Minimizing Variations in Bioavailability of Ezetimibe," ***Colloids. Surf. B Biointerfaces*****,** 76, 410.

5. Constantinides, PP (1995), "Lipid microemulsions for improving drug dissolution and oral absorption: physical and biopharmaceutical aspects," ***Pharm Res.***, 12, 1561.
6. Pouton, CW (2000), **"**Lipid formulations for oral administration of drug non-emulsifying, self-emulsifying and self-microemulsifying drug delivery system," ***Eur. J. Pharm. Sci.***, 2, S93.
7. Pouton, CW (1985), "Self-emulsifying drug delivery systems: assessment of the efficiency of emulsification," ***Int J Pharm***., 27, 335.
8. Patil, P; Joshi, J and Paradkar, P (2004), "Effect of formulation variables on preparation and evaluation of gelled self-emulsifying drug delivery system (SEDDS) of ketoprofen," ***AAPS Pharm Sci Tech***., 5, 34.
9. Gursoy, RN and Benita, S (2004), "Self-emulsifying drug delivery systems (SEDDS) for improved oral delivery of lipophilic drugs," ***Biomed Pharmacother.***, 58, 173.
10. Kawakami, K; Yoshikawa, T; Moroto, Y; Kanaoka, E; Takahashi, K and Nishihara, Y *et al.* (2002), "Microemulsion formulation for enhanced absorption of poorly soluble drugs. I. Prescription design," ***J. Cont. Rel.***, 81, 65.
11. Georgakopoulos, E; Farah, N and Vergnault, G (1992), **"**Oral anhydrous nonionic microemulsions administrated in softgel capsules," ***B T Gattefosse***, 85, 11.
12. Huibers, PTD and Shah, DO (1997), "Evidence for synergism in nonionic surfactant mixtures: Enhancement of solubilization in water-in-oil microemulsions," ***Langmuir***, 13, 5762.
13. Kang, BK; Lee, JS; Chon, SK; Jeong, SY; Yuk, SH; Khang, G; Lee, HB and Cho, SH (2004), "Development of self-microemulsifying drug delivery systems (SMEDDS) for oral bioavailability enhancement of simvastatin in beagle dogs," ***Int J Pharm***., 274, 65.
14. Kommuru, TR; Gurley, B; Khan, MA and Reddy, IK (2001), "Self-emulsifying drug delivery systems (SEDDS) of coenzyme Q10: formulation development and bioavailability assessment," ***International Journal of Pharmacy***, 212, 233.
15. Langer, RS and Wise, DL (1984), "***Medical Applications of Controlled Release, Applications and Evaluation***, I&II," CRC Press, *Boca Raton, Florida*.
16. Meinzer, A; Mueller, E and Vonderscher, J (1995), "Microemulsion a suitable galenical approach for the absorption enhancement of low soluble compounds," ***B T Gattefosse***, 88, 21.
17. Moffat, AC (1986), "Clarke´s isolation and identification of drugs," ***Pharmaceutical Press, London.***
18. Nepal, PR; Han, HK and Choli, HK (2010), "Preparation and In vitro – In vivo Evaluation of Witepsol H35 Based SNRDDS of Coenzyme Q (10)," ***Eur. J. Pharm. Sci.***, 39, 224.
19. Nielsen, FS; Gibault, E; Ljusberg-Wahren, H; Arleth, L; Pedersen, JS and Mullertz, A (2007), "Characterization of Prototype SNEF of Lipophilic Compounds," ***J. Pharm. Sci***. 96, 876.
20. Patil, P; Vandana, P and Paradkar, P (2007), "Formulation of selfemulsifying drug delivery system for oral delivery of simvastatin: In vitro and in vivo evaluation," ***Acta pharma***., 57, 111.
21. Pillai, O; Dhanikula, AB and Panchagnula, R (2001), ***Current Opinion in Chemical Biology***, 5, 439.
22. Pouton, CW (1997), "Formulation of self-emulsifying drug delivery systems," ***Adv. Drug Del. Rev.***, 25, 47.
23. Shafiq, S**;** Faiyaz, S; Sushma, T; Farhan,, JA; Khar, RK and Ali, M (2007), "Development and bioavailability assessment of ramipril nanoemulsion formulation," ***Eur. J. Pharm. Biopharm.***, 66, 227.
24. Tamilvanan, S (2004), "Oil-in-water Emulsions- Implications for Ocular and Parentral Drug Delivery Systems," ***Progress in Lipid Research.***
25. Toguchi, H; Ogawa, Y and Shimamoto, T (1990), **"**Effects of the physicochemical properties of the emulsion formulation on the

bioavailability of ethyl 2-chloro-3-(4-(2-methyl-2-phenylpropyloxy) phenyl) propionate in rats," ***Chem Pharm Bull***., 38, 2797.

26. Yoon, KA and Burgess, DJ (1996), "Effect of non-ionic surfactant on transport of model drug in emulsions," ***Pharm Res***., 13, 433.

Correspondence Author:
S.L. Harikumar
Department of Pharmaceutics, Rayat and Bahra Institute of Pharmacy,
Sahauran, Distt. Mohali, Punjab, India-140104
Email: slharikumar@gmail.com

Cite This Article: Gurjeet, Kaur; Pankaj, Chandel and SL, Harikumar (2013), "Formulation Development Of Self Nanoemulsifying Drug Delivery System (SNEDDS) Of Celecoxib For Improvement Of Oral Bioavailability", ***Pharmacophore***, Vol. 4 (4), 120-133.