IJPSR (2012), Vol. 3, Issue 07 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 26 March, 2012; received in revised form 23 April, 2012; accepted 17 June, 2012

SOLUBILITY ENHANCEMENT OF CANDESARTAN CILEXETIL BY SELF EMULSIFYING DRUG DELIVERY SYSTEMS

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Keywords:
Candesartan,
Surfactants,
Lipid vehicles,
SEDDS,
Pseudoternary phase diagrams,
Zeta potential,
Freeze-Thawing

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ABSTRACT

The present research work was aimed at the enhancement of solubility of Candesartan by Self Emulsifying Drug Delivery Systems (SEDDS). Candesartan is a BCS class II drug having low aqueous solubility and high permeability; hence its bioavailability is solubility rate limited. The saturated solubility of Candesartan in various oils and surfactants was determined. The excipients were screened and selected showing maximum solubility and compatibility for Candesartan. SEDDS formulations of Candesartan were developed using different Oils, Surfactants and Co-Surfactant combinations. Pseudoternary phase diagrams were constructed using Triplot V 4.1.2 software and applying Pseudoternary phase diagrams, microemulsification area was evaluated. Formulations were prepared based on phase diagrams using various proportions of oil, surfactants and co-surfactants. The formulations were screened visually for stability and phase separation. Seven formulations were selected for further evaluations like effect of dilution, freeze-thawing, emulsion droplet size and zeta potential. Among the seven formulations three were optimized and filled in hard gelatin capsules. The *in-vitro* dissolution studies of the SEDDS formulation were performed and the dissolution rate of SEDDS was compared with plain Candesartan (API). The results indicated that the solubility and dissolution rate of Candesartan was significantly higher than that of plain drug (API). The results of the present studies demonstrate that SEDDS can be used as a potential means for improving solubility, dissolution and bioavailability of Candesartan.

INTRODUCTION: Most of the new chemical entities (NCE) developed today are sparingly soluble in water and suffer with poor bioavailability. The properties of new chemical entities are shifting towards higher molecular weight and high lipophilicity resulting in poor aqueous solubility. Due to poor aqueous solubility, many drug candidates become unsuccessful to reach the market in spite of exhibiting potential pharmacodynamic activity. Further, poorly water soluble drugs are administered at much higher individual doses than actually desired to achieve necessary plasma levels.

The therapeutic efficacy and bioavailability of any drug depends upon the solubility of drug. Solubility of drug is one of the important parameter to achieve to attain the desired concentration of drug in systemic circulation for the pharmacological response. Therefore, strategies to improve the aqueous solubility and the release rate of drugs are employed and are under constant investigation.

Various formulation strategies have been reported to enhance the solubility of drugs, these includes, particle size reduction [1], pH adjustment [2], co-solvency [3],

complexation [4], solid dispersions [5], SEDDS [6] etc., However each technique has its own advantages and limits. Among all these techniques SEDDS appear to be potential method for the solubility enhancement due to its ease of formulation and evaluation.

SEDDS are well known for their potential to enhance the solubility of hydrophobic drugs and consists of isotropic mixtures of an oily vehicle, surfactants, co-surfactants and thickening agents. SEDDS require very less energy to emulsify, and so they undergo spontaneous emulsification in the lumen of gut up on dilution in aqueous phase under the gentle agitation provided by the GI motility. The microemulsions so formed are easily absorbed from the gastrointestinal tract through the villi as chylomicrons. Selection of suitable SEDDS depends on (1) solubility of Candesartan in various excipients (2) area of self-emulsifying region in the phase diagram (3) time required for self-emulsification (4) droplet size distribution of emulsion (5) thermodynamic stability of emulsions [7, 8].

Candesartan is an antihypertensive drug. Candesartan is a Biopharmaceutics Classification System (BCS) Class II drug. Candesartan is a lipophilic drug with a low aqueous solubility. Thus, the low oral bioavailability of Candesartan is due to its solubility and dissolution limitations. The absorption of Candesartan is increased by the presence of food in the gastro intestinal tract. Hence SEDDS seemed to be an option for enhancement of solubility of Candesartan.

Candesartan is available in various doses (2 mg, 4 mg, 8 mg, 16 mg, and 32 mg). For our study we selected 8 mg as the working dose to limit the total formulation volume. The main objective of the study was to enhance the solubility of Candesartan by formulating an optimal SEDDS formulation and to evaluate various *in-vitro* characteristics.

MATERIALS AND METHODS

Materials: Candesartan was procured from Hetero Drugs Pvt. Ltd. (Hyderabad, India). Labrafac PG, Lipophile 1349, Peceol, Labrasol, Cremophor RH40, Transcutol P, Capryol 90, Lauroglycol 90, Plurol Oleique was donated by Gattefosse (Mumbai, India). Tween 80, PEG 400, and castor oil were purchased from Merck (Mumbai, India).

HPLC grade Methanol, Acetonitrile, water, and Potassium Bromide used in the present study were bought from Merck (Mumbai, India).

Methods:

Solubility studies [9, 10]: The saturation solubility of Candesartan was determined in various oils, surfactants and co-surfactants by adding excess amount of drug to each screw capped glass vials containing 1 gram of vehicle. The mixture was subjected to cyclomixing using cyclo-mixer to facilitate drug solubilisation. Then, the mixtures were shaken in an orbital shaker for 72 hours at 25^{o} C. After reaching equilibrium, each vial was centrifuged at 2000 rpm for 15 min. The supernatant was collected and filtered using 0.45µ filters. The aliquots of supernatant were diluted with mobile phase and the concentration of drug was quantified by using HPLC method, as reported in the analytical method.

HPLC Analysis: Candesartan was analyzed by SHIMADZU Prominence LC 20 AD series with UV detection. Data acquisition system was LC Solutions. The chromatographic conditions are

Column : Phenomenex (C-18 250×4.6 mm, 5µ)

Column temperature : Room temperature

Flow rate : 1ml/min

Mobile phase : Acetonitrile (70): 5mM Sodium Acetate Buffer (30), pH - 3.5 to 4

Run time : 15 min

Type of flow : Isocratic

UV wavelength: 254 nm

Pseudoternary Phase Diagrams: To investigate the micro-emulsion region, the pseudo-ternary phase diagrams of oil, surfactant/co-surfactant, and water were constructed by a water titration method at Room Temperature. The surfactant (Cremophor RH40) was blended with a co-surfactant (Transcutol HP or Labrasol) in a fixed volume ratio 4:1, 3:1, 2:1 and 1:1 respectively. Aliquots of surfactant/co-surfactant mixture were then mixed with the oil (Labrafac Lipophile WL 1349) at volume ratios of 9:1, 8:2, 7:3,

6:4, 5:5, 4:6, 3:7, 2:8, 1:9 in different vials. The vials were vortexed for sufficient time to attain uniformity. A small amount of water in 5% increment was added into each vial and mixed with vortex. The samples set aside to attain the equilibrium. The equilibrated samples were checked visually, and classified as clear microemulsion, coarse emulsion and gel phases. The percentage of surfactant, cosurfactant, oil and water used herein was decided on the basis of the requirements for the spontaneously emulsifying systems and pseudo ternary phase diagrams were plotted using TriPlot Version 4.1.2 Software.

Preparation of SEDDS Formulations: A series of SEDDS formulations were prepared using Labrasol and Transcutol HP as the Co Surfactants, Cremophor RH 40 as Surfactant and Labrafac Lipophile WL 1349 as the oil. In all the formulations, the level of Candesartan was kept constant (i.e., 8mg). Surfactant/Co Surfactants mixture was prepared by mixing in suitable proportions and vortexed. Accurately weighed amount of Candesartan was dispersed in Labrafac Lipophile WL1349 and surfactant/co surfactant mixture was added to it. The components were mixed by gentle stirring and vortex mixing. The mixture was stored at room temperature for further use.

Emulsification time and Stability studies of Formulations: Self-emulsifying properties of SEDDS formulations were evaluated by visual assessment. The time taken for the formation of micro emulsion was determined by drop wise addition 1gram of the Formulation into 500 ml of distilled water and SGF in a separate glass beakers at 37°C, and the contents were stirred using magnetic stirrer at ~100 rpm.

The tendency to form an emulsion was judged as **"good"** when droplets spread easily in water and formed a fine emulsion that was clear or transparent in appearance, and it was judged **"bad"** when the corresponding performance was poor or there was less clear emulsion formation. Depending on visual appearance and time taken for Self emulsification, formulations were graded as:

- **Grade I:** Rapidly emulsifying with clear or bluish appearance
- **Grade II:** Rapidly emulsifying with slightly less clear and with a bluish white appearance
- **Grade III:** Slowly emulsifying fine milky emulsion
- **Grade IV:** Slowly emulsifying Dull, grayish white appearance

Effect of Dilution: Selected formulations were subjected to dilution in different ratios of 1:10, 1:50, 1:100 and 1:1000 fold dilution with distilled water, 0.1 N HCl and phosphate buffer (pH 6.8). The diluted emulsions were stored for 24 h and monitored for any physical changes (such as precipitation or phase separation).

Freeze Thawing: The objective of thermodynamic stability is to evaluate the phase separation and effect of temperature variation on SEDDS formulation. Formulations were diluted with deionized water (1:20) and centrifuged at 15,000 rpm for 15 min, and formulation was observed visually for phase separation. Formulations that did not show any sign of phase separation after centrifugation were subjected to freeze thaw cycle. In a freeze thaw study, Candesartan SEDDS was diluted with deionized water (1:20) and two freeze thaw cycle between (−20°C and +25°C) with storage at each temperature for not less than 4 hours were done for formulations.

Emulsion Droplet Size Analysis: SEDDS formulations were diluted to 100 times with distilled water in beaker with constant stirring on a magnetic stirrer. The droplet size distributions and Zeta potential of resultant microemulsion were determined after 1 hour by Zetasizer Version 6.01 (Malvern Instruments, UK). Size analysis was performed at 25ºc by placing in an electrophoretic cell with an angle of detection of 90ºC for measurement.

***In-vitro* Dissolution Studies:** *In-vitro* drug release studies of Selected SEDDS were performed using USP Type II dissolution apparatus. The dissolution medium consisted of 900 ml of 0.1N HCl, pH 1.2 (SGF). No enzymes were added to the dissolution media Liquid filled Capsules containing 8 mg of Candesartan was introduced into the dissolution medium. At predetermined time intervals 5ml of aliquot was withdrawn, filtered using 0.45µm syringe filter and an equivalent volume of fresh dissolution medium was immediately added. The amount of drug released was estimated by measuring absorbance at 275 nm using a Double beam spectrophotometer.

Dissolution of Physical mixture (10%API+90% Inert Diluent i.e., Lactose) was also determined in identical manner.

RESULTS AND DISCUSSIONS:

Solubility studies: Solubility of drug in lipid excipients is the most important criteria for the selection of excipients for the development of SEDDS formulation. The solubility of Candesartan in various oils, surfactants and co-surfactants are summarized in **figure 1, 2 and 3.** The solubility of Candesartan in oils was found to be maximum in Labrafac Lipophile WL 1349 and in surfactants the highest solubility was found in Cremophor RH40 and in co-surfactants the highest solubility was in Transcutol HP.

Screening and Compatibility studies of Excipients: IR spectra of pure drug Candesartan (figure 4)) show characteristic absorption at 2941cm^{-1}, 1752 cm^{-1}, 1714 cm^{-1} and 1614 cm^{-1}. This absorption peak at 2941 cm^{-1} is due to stretching of C-H bond, the peaks at 1752 cm^{-1} and 1714 cm^{-1} are due to two C-O bonds (carbonyl group) and peak at 1614 cm^{-1} is due to C-N bond. These peaks are present in IR scan of all formulations, so it confirms that, presence of undisturbed drug in the formulations. However, the retention times of the drug solubilized in various excipients was similar to that of pure drug chromatograms. Hence, there are no drug-excipient interactions.

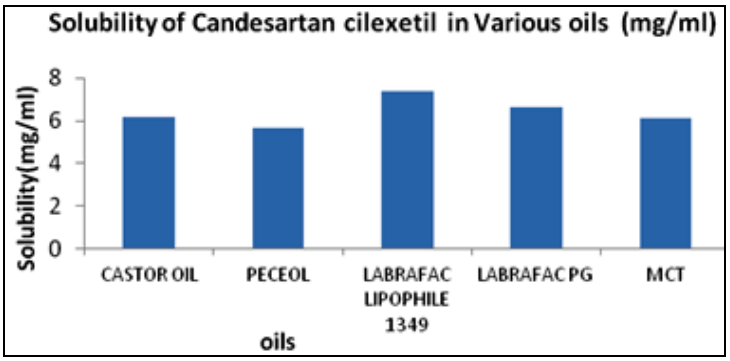

FIGURE 1: SOLUBILITY OF CANDESARTAN IN OILS

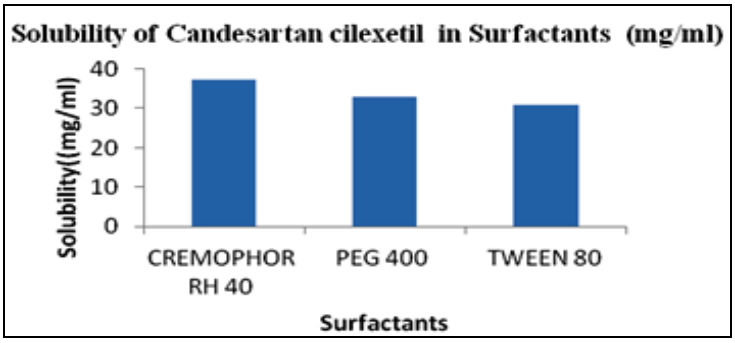

FIGURE 2: SOLUBILITY OF CANDESARTAN IN SURFACTANTS

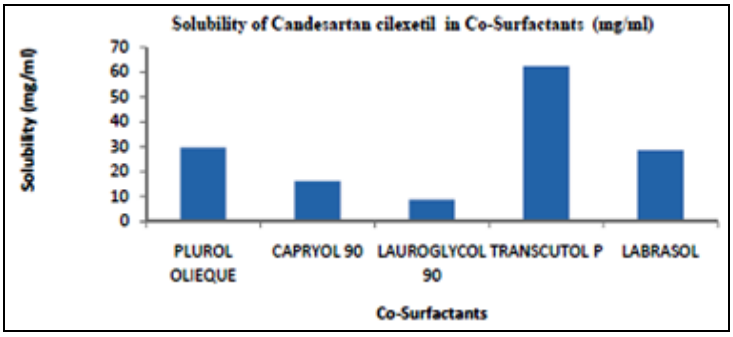

FIGURE 3: SOLUBILITY OF CANDESARTAN IN CO-SURFACTANTS

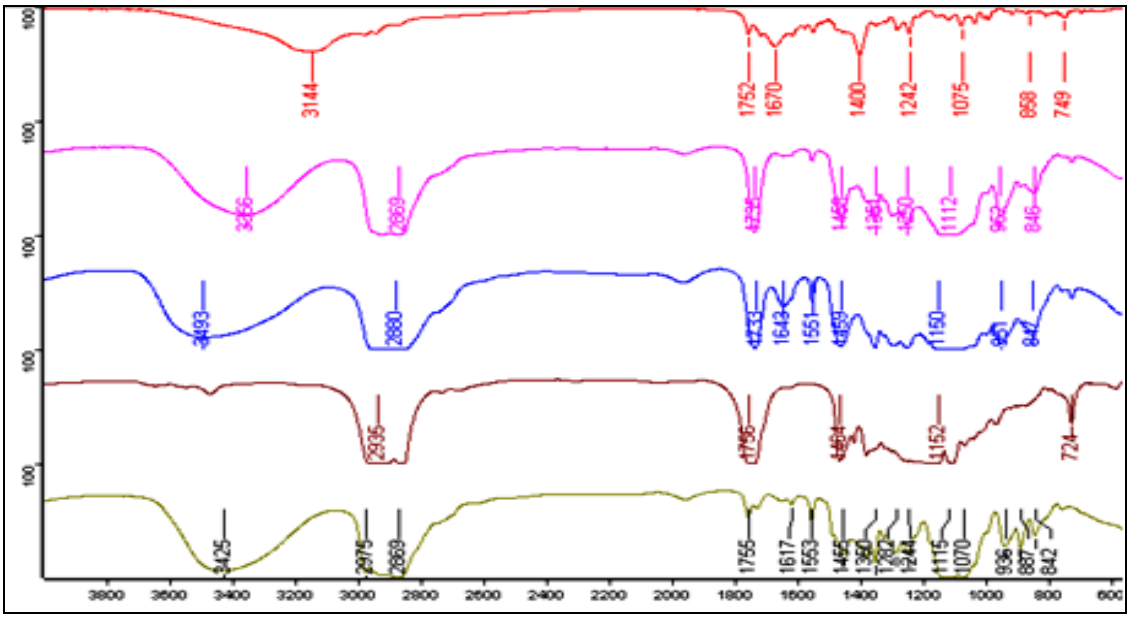

FIGURE 4: IR SPECTRUMS OF PLAIN CANDESARTAN (a), Candesartan in Labrasol (b), Candesartan in Cremophor RH40 (c), Candesartan in Labrafac Lipophile WL 1349 (d) and Candesartan in Transcutol P (e)

Preparation of Formulations: From the solubility and IR spectroscopy studies, the formulations were formulated for the further studies. The formulations and their compositions are given in **table 1**.

TABLE 1: TABLE SHOWING VARIOUS FORMULATIONS AND THEIR COMPOSITIONS SELECTED

Formulation Name	Surfactant	Co-surfactant	Surfactant – cosurfactant ratio (S:Sco)	Oil
LLCT11	Cremophor RH 40	Transcutol HP	1:1	Labrafac Lipophile WL1349
LLCT21	Cremophor RH 40	Transcutol HP	2:1	Labrafac Lipophile WL1349
LLCT31	Cremophor RH 40	Transcutol HP	3:1	Labrafac Lipophile WL1349
LLCT41	Cremophor RH 40	Transcutol HP	4:1	Labrafac Lipophile WL1349
LLCL11	Cremophor RH 40	Labrasol	1:1	Labrafac Lipophile WL1349
LLCL21	Cremophor RH 40	Labrasol	2:1	Labrafac Lipophile WL1349
LLCL31	Cremophor RH 40	Labrasol	3:1	Labrafac Lipophile WL1349
LLCL41	Cremophor RH 40	Labrasol	4:1	Labrafac Lipophile WL1349

Pseudoternary Phase Diagrams: Pseudoternary phase diagrams (**figure 5, 6**) were constructed for each surfactant/co-surfactant combination. The self emulsification region was determined by visual observation for spontaneity of emulsification, clarity, colour and stability. From the phase diagrams (figure 5, 6) it was inferred that increase in oil content increased the particle size proportionally and resulted in coarse emulsions. oil and surfactant mixture ratios 9:1, 8:2, 7:3, 6:4, 5:5 and 4:6, formed milky white emulsions. . Microemulsion obtained at Oil: Smix ratio 3:7 and 2:8. For 1:9 composition of oil and surfactant mixture clear emulsion has formed but its flowability was very poor. Microemulsion region was observed in the formulations made of 10-30% oil content. The maximum self-microemulsifying region expanded with increasing amounts of surfactant (Cremophor RH 40) and was maximum at 2:1, 3:1, 4:1.

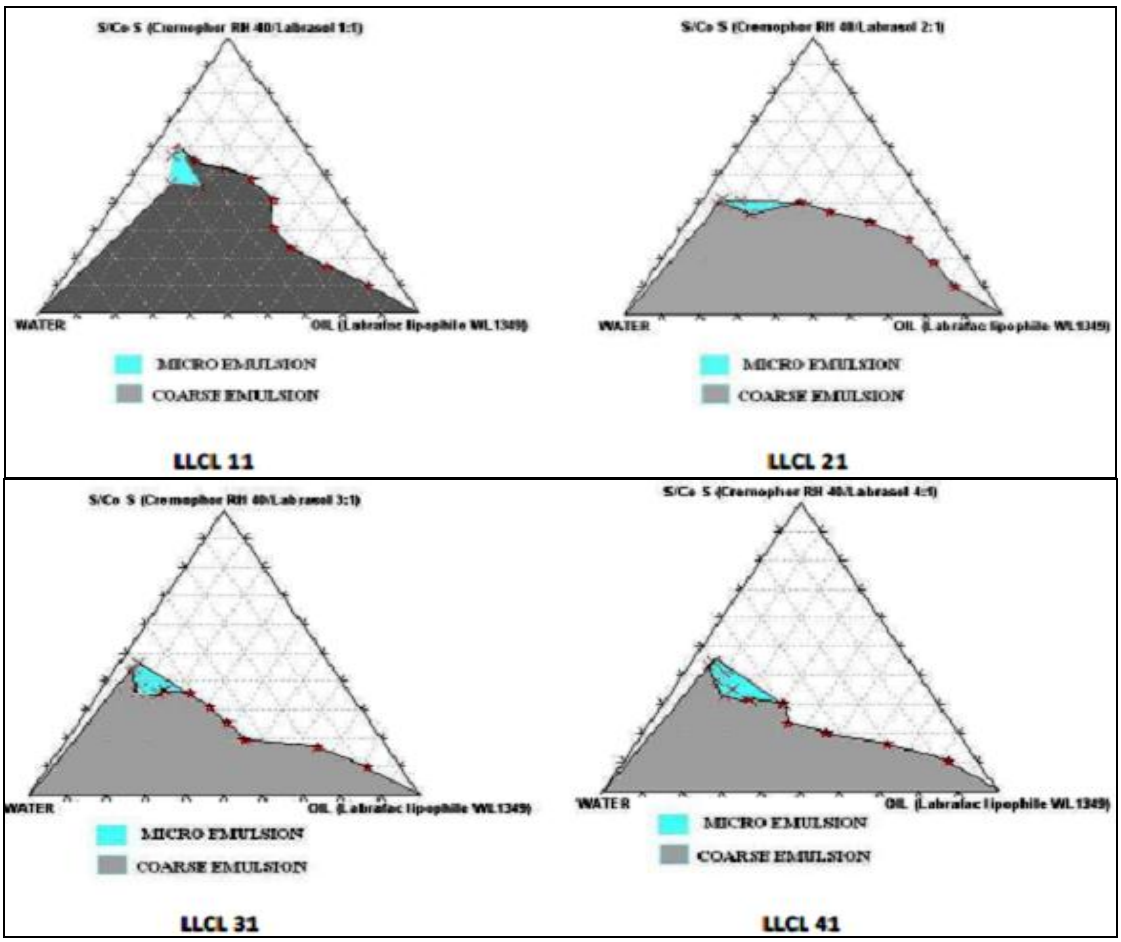

FIGURE 5: PSEUDO TERNARY PHASE DIAGRAMS OF FORMULATION LLCL AT DIFFERENT SURFACTANT/CO-SURFACTANT RATIOS (1:1, 2:1, 3:1, 4:1). The light blue color indicates the micro emulsion region

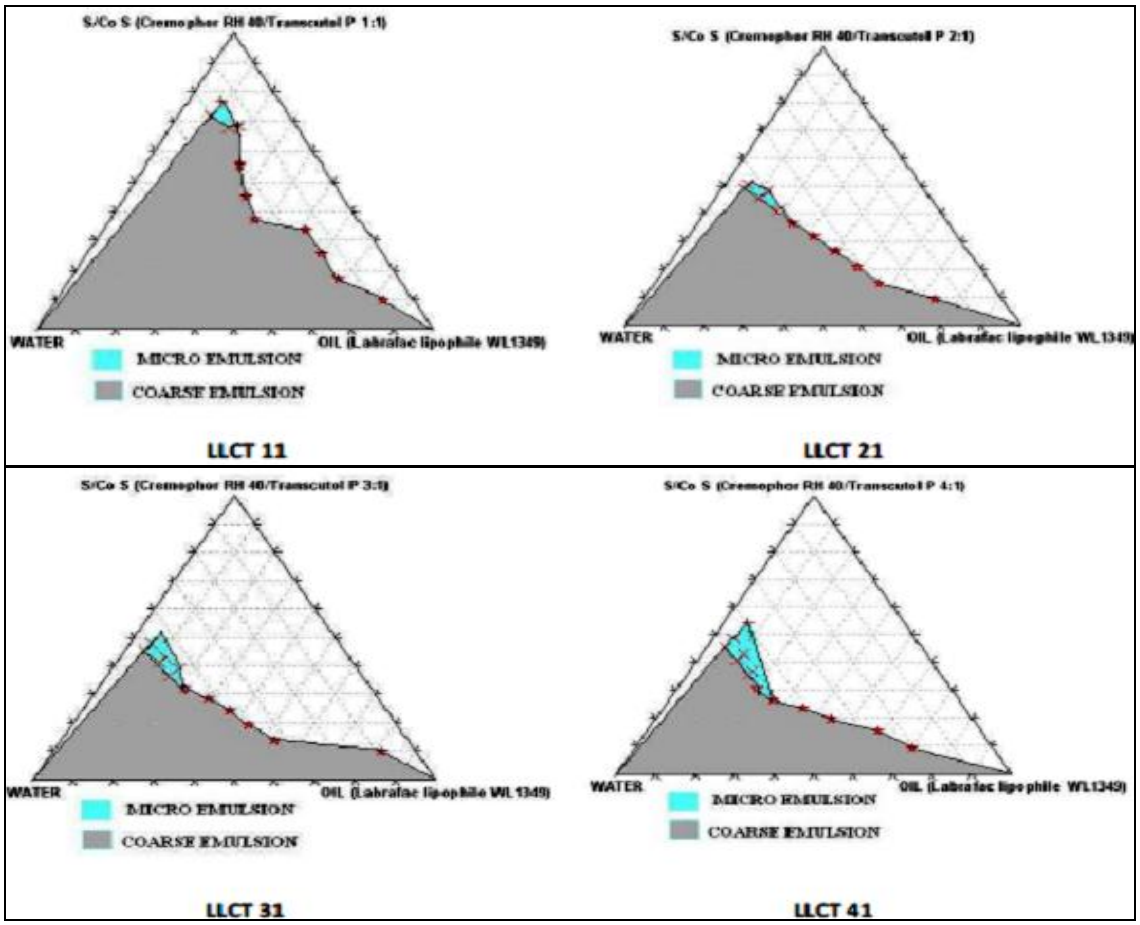

FIGURE 6: PSEUDO TERNARY PHASE DIAGRAMS OF FORMULATION LLCT AT DIFFERENT SURFACTANT/CO-SURFACTANT RATIOS (1:1, 2:1, 3:1, 4:1). The light blue color indicates the micro emulsion region.

From the phase diagrams the following formulation compositions were selected for further studies they are LLCT21-2, LLCT31-2, LLCT41-2, LLCL21-2, LLCL31-2, LLCL31-3 and LLCL41-2.

TABLE 2: TABLE SHOWING THE SELECTED SEDDS FORMULATIONS AND THEIR COMPOSITIONS

Formulation Name	Drug (w/w%)	Labrafac Lipophile WL1349 (w/w %)	Cremophor RH 40 (w/w%)	Labrasol (w/w%)	Transcutol HP (w/w%)
LLCT21-2	1.6	19.68	52.41	-	26.31
LLCT31-2	1.6	19.68	59.04	-	19.68
LLCT41-2	1.6	19.68	62.98	-	15.74
LLCL21-2	1.6	19.68	52.48	26.34	-
LLCL31-2	1.6	19.68	59.04	19.68	-
LLCL31-3	1.6	29.52	51.66	17.22	-
LLCL41-2	1.6	19.68	62.98	15.74	-

TABLE 3: TABLE SHOWING THE *IN-VITRO* CHARACTERIZATION OF SELECTED SEDDS FORMULATIONS

Formulation Name	Grade	Self-emulsification time (sec)	Stability	Effect of dilution	Freeze-thawing	Z-Average (r.nm)	Zeta Potential (mV)
LLCT21-2	I	45.66±2.13	Pass	Pass	Pass	20.85	-12.4
LLCT31-2	I	51.33±1.70	Pass	Pass	Pass	22.82	-14.8
LLCT41-2	I	50.45±2.15	Pass	Pass	Pass	20.98	-12.9
LLCL21-2	I	42.76±1.08	Pass	Pass	Pass	19.4	-12.9
LLCL31-2	I	46.33±2.52	Pass	Pass	Pass	19.26	-12.6
LLCL31-3	I	52.66±3.52	Pass	Pass	Pass	32.63	-19.3
LLCL41-2	I	51.66±1.42	Pass	Pass	Pass	40.88	-10.6

Droplet Size Analysis: The droplet size distribution (Z-average) of various formulations and their Zeta Potential is given in Table 3. The compositions LLCL21-2, LLCT31-2 and LLCT41-2 were finally selected based on their size, zeta-potential and visual observation as potential SEDDS formulations of Candesartan.

***In Vitro* Dissolution Studies:** Dissolution studies of above formulations were performed and the drug release from SEDDS was compared with plain drug (API). The results are shown in **figure 7**. The results revealed that all SEDDS formulations showed an improved drug release of above 80% and that the plain showed a drug release of 32% at the end of 90 minutes.

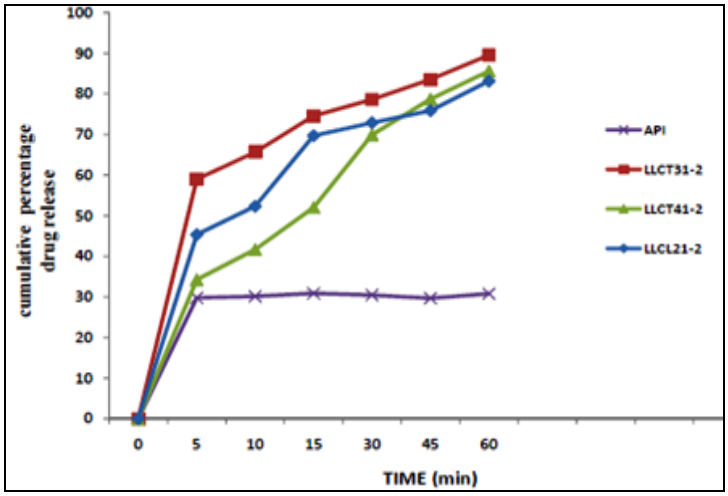

FIGURE 7: COMPARATIVE RESULTS OF DRUG RELEASE FROM PLAIN CANDESARTAN AND SEDDS FORMULATIONS

CONCLUSION: An optimized SEDDS formulations consisting of Candesartan, Labrafac Lipophile WL1389, Labrasol, Transcutol HP and Cremophor RH40 were successfully developed. The developed formulations showed an increased solubility, dissolution rate and bioavailability of Candesartan. Further the formulations were found to be thermodynamically stable, for dilution, freeze-thawing and centrifugation. None of the formulations showed drug precipitation or phase separation. The dissolution profiles of all the 3 formulations selected showed a drug release of greater than 80% in 90 minutes. Among all the formulations LLCT 31-2 showed a maximum drug release of 89.5% in 90 minutes. Thus our study confirmed that the SEDDS formulations can be potentially used as an alternative to the traditional oral formulations for the poorly soluble drugs like Candesartan to improve its solubility and dissolution.

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How to cite this article:
Reddy M. Sunitha *, Goud P. Srinivas and Apte S. S.: Solubility Enhancement Of Candesartan Cilexetil By Self Emulsifying Drug Delivery Systems. *Int J Pharm Sci Res*, 2012; Vol. 3(7): 2098-2104

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