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SDC-PC BASED SOLID SEDDS OF BCS CLASS III DRUG

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ABSTRACT

Aim: The purpose of this research is to develop, optimise, and analyse losartan potassium loaded solid SEDDS using a newly synthesised surfactant. Losartan potassium is an angiotensin II receptor blocker that belongs to the BCS class III of antihypertensive drugs. Solid SEDDS were used to increase the permeability, oral bioavailability, and first pass metabolism of losartan potassium, which had a low permeability and oral bioavailability. **Material and methods:** As a surfactant, SDC-PC was synthesized. The solubility of the API in various oils, surfactants, and co-surfactants was investigated, and oleic was chosen as the oil phase, SDC-PC as the surfactant, and PEG 400 as a co-surfactant for formulation. A pseudo-ternary phase diagram was created to get the ideal emulsification area. SEDDS liquid was prepared and tested. Following an evaluation, it was discovered that LP4 was stable and optimum. **Result and discussion:** Aerosil 200 was used as a carrier to convert the formulation into solid SEDDS. The formulations were compared to LOSAR®, as marketed product. On in-vitro drug release, optimised batch LP4 was shown to have similar drug release to the marketed formulation.

KEYWORDS: Losartan potassium, SEDDS, Surfactant, Solid dosage form, Pseudo-ternary phase diagram.

INTRODUCTION

Losartan potassium (LP) is a non-peptide angiotensin II receptor antagonist (Type AT1) that is orally active and undergoes substantial first-pass metabolism by the cytochrome P450 enzyme, with 14 % of the dose converting to an active metabolite.[1,2] LP is a class III drug that comes in the form of a white to off-white free-flowing crystalline powder with a log P value of 5.37, a half-life of about 2 hours, and a systemic bioavailability of about 33%.[1,2,3] The drug is used once or twice a day as a 25 mg tablet, with total daily doses ranging from 25 to 100 mg.[2] In diabetic patients, LP provides beneficial pressure control, lowering the risk of stroke and the progression of renal disease to the terminal stage.[4] LP binds to plasma proteins extensively and can cause gastrointestinal problems, neutropenia, active hepatotoxicity, migraines, and pancreatitis.[5] To reduce the frequency of dose and adverse effects of LP, sustained drug delivery is required to prolong the drug release, and self-emulsifying drug delivery can be employed to achieve this.[3]

Self emulsifying formulations are defined as isotropic mixtures of natural or synthetic oil, liquid or solid surfactant or one or more hydrophilic solvents and co-solvent or surfactants.[6] Upon mild agitation followed by dilution in aq-media, such as GI fluids, these system can form oil-in-water(o/w) emulsion(10-100nm).[7] SEDDS' physical qualities, as well as the chemical structures of its constituents, were found to be important determinants of application and tolerability.[8] These fine microemulsion droplets have the benefit of providing the drug in a dissolved form with a large interfacial surface area for drug absorption, resulting in improved, uniform, and repeatable bioavailability.[9] The oral bioavailability of both hydrophobic and hydrophilic drugs can be improved by increasing membrane fluidity to facilitate transcellular absorption, opening tight junctions to allow paracellular transport, inhibiting cytochrome P450 as isoenzyme in the intestinal region, and inhibiting efflux pumps such as P-glycoprotein.[10] Using a self-emulsifying drug delivery system to improve oral bioavailability of BCS class III medicines has a ton of potential. These systems have been found to be useful in the formulation of first-pass metabolism medications as well as orally delivered pharmaceuticals that obtain access to the systemic circulation through direct absorption into the intestinal lymphatic system.[11]

Following mechanisms are implicated for the improvement of permeability.

- Gastric retention time – The oil in SEDDS can decrease the gastric empting time.

- Lymphatic transport – The oil in SEDDS may enhance the lymphatic transport and the bioavailability of highly lipophilic drugs by promoting their association with chylomicrons in the enterocytes and avoiding hepatic metabolic pathway.
- Intestinal protein efflux – oil and non-ionic surfactants in SEDDS may reversibly inhibit P-glycoprotein and the multidrug resistance related proteins -2 efflux transport or increases the transcellular permeability.
- First pass metabolism – SEDDS may inhibit the action of cytochrome P450 enzyme which metabolizes drug in intestinal wall.[12]

Because liquid SEDDS have disadvantages including instability, low convenience, production processes, interaction during filling in capsule shells, and storage temperature, solid SEDDS were developed. When compared to precursor liquid SEDDS, solidification provides a number of advantages, which can be summarised as better drug solubility and dissolution, improved safety, controlled or sustained drug release, and industrial and commercial benefits.[13]

The aim of our present study to develop, optimize and evaluate losartan potassium loaded solid SEDDS using synthesized surfactant. As surfactant plays important role to reduce surface tension between two different phases. The vesicular based system act as reservoir for the control release of a number of active drug including antibiotics, corticosteroids. They also act as permeation enhancer in systemic absorption.[14]

MATERIALS AND METHODS

Losartan potassium was obtained from YARROW CHEM PRODUCTS, Mumbai. Oleic acid was obtained from S. D. Lab chemical centre, Mumbai. Aerosil 200 was obtained from Gangwal chemical, Mumbai. Stearoyl chloride was obtained from Dolphin pharmacy instrument Pvt. LTD, Mumbai. Sulfanilamide, acetone, n-hexane, ethyl acetate, caster oil, iso propyl myristate, PEG 400, Tween 80. all the chemicals and solvents used in this work belonged to analytical grade.

Synthesis of surfactat

N-((4-sulfamoylphenyl) carbamothioyl) stearamide (SDC-PC) was synthesized by taking stearoyl chloride 0.67 mL (2 mmol) and KSCN 194 mg (2 mmol) in 50 mL round bottom flask equipped with reflux condenser in 20 mL acetone. The resulting mixture was then stirred for 2 hours at 60 °C. After 2 hours, Sulfanilamide 344 mg (2 mmol) was added and

refluxed the reaction mixture for further 18 hours (Scheme 1). The progress of the reaction was monitored periodically using TLC in ethyl acetate and n-hexane (3:7, v/v) solvent system.[14]

Evaluation of synthesized surfactant

% Practical yield

Percent practical yield was calculated by following formula:

% practical yield = $\text{Practical yield} \div \text{Therotical yield} \times 100$

Melting point

Melting point apparatus was used to determine the melting point of SDC-PC. In the melting point apparatus, a little amount of SDC-PC was inserted in one end of a closed capillary and the temperature at which the drug melted was recorded and compared to previous research.

ATR-FTIR Spectroscopy

The ATR-FTIR spectrum of surfactant was collected using the ATR-FTIR instrument BRUKER-Alpha 100508. A small amount of drug was collected and applied directly to the ATR diamond. A pressure pump was used to push the medication. The spectrum was obtained by combining 24 scans across a range of 4000-400cm.[15] The precise wavelength of light was partially absorbed by the sample, and at least one was reflected off the internal surface in contact with the sample. The ATR-FTIR spectrum depicts percent transmittance in terms of light wavelength (cm). For all interaction, the spectrum of the sample was acquired and compared to the spectrum of the pure drug.[16]

Critical Micelles Concentration (CMC) Determination

The CMC of all the newly synthesized surfactants were determined spectrophotometrically using UV-visible spectrophotometer (Shimadzu, UV-1800, Japan). Surfactant were dissolved in ethanol in different concentrations i.e. 0.01–0.1 mM read spectrophotometrically. A plot for each concentration versus its absorption was made and then straight lines were drawn on the values. The critical micelle concentration was the point where two straight lines intersect each other on this graph of concentration vs absorption.[14]

Solubility study

Solubility studies in various oils, surfactants, and co-solvents were conducted in order to determine the optimal SEDDS excipients with good solubilizing capacity for losartan

potassium.[17] In a glass vail containing an excess of Losartan potassium, one (1) ml of each of the selected oil, surfactant, and co-surfactant sample was added (50-70 mg). To achieve equilibrium, the vails were shaken for 72 hours on an orbital shaker at 40 ° C. After that, aliquots of the supernatants were taken and filtered using a 0.45m membrane filter. Filtration with a 0.45m membrane filter separated the unmixed drug. The filtered sample was centrifuged for 15 minutes at 3000 rpm.

Construction of ternary phase diagram

Phase diagram provide useful platform for delineating the area of microemulsion. Ternary phase diagrams of oil, surfactant/co-surfactant (Smix) and water were developed using the water titration method.[19] Surfactant and co-surfactant were mixed up with six different (Km) weight ratios 1:9 to 9:1. For each phase diagram oil to specific Smix ratio was mixed in different proportion from 0.5:4.5 to 4.5:0.5. Nine different proportions are 0.5:4.5, 4:1, 3.5:1.5, 3:2, 2.5:2.5, 2:3, 1.5:3.5, 4:1 and 4.5:0.5. This made to maximum ratios were covered for the study to delineate the boundaries of phase precisely formed in the phase diagram. A transparent and homogenous mixture of oil/Smix was formed by using magnetic stirring. Then each mixture was titrated with drop wise addition under gentle agitation until the required clarity and flow ability was achieved. The point at which system become turbid, these points were recorded. Corresponding to these points calculate the % w/w combination of oil, surfactant and co-surfactant. Using these points phase diagram was constructed to determine the boundaries of microemulsion reason.[20] The phase diagram constructed using CHEMIX school software version 7.0.

Preparation of liquid SEDDS

By dissolving the amount of Losartan potassium as shown in the ternary phase diagram, a number of SEDDS formulations were created. The oil phase (125 mg) was placed in a vial, and the drug (25 mg of LP) was added straight to this vial and combined using a vortex mixer. To make an isotropic mixture, a sufficient amount of Smix was added to the oil-drug mixture and vortexed, followed by homogenization for 10 minutes. The formulation was checked for turbidity and phase separation before being stored at room temperature until further use.[21]

Evaluation of liquid SEDDS

Thermodynamic stability study

Heating cooling cycle (Freeze-thaw cycle): Six cycles of heating at 45˚C (incubator) and cooling at 4˚C (refrigerator) was conducted for not less than 48hrs at each temperature.

Centrifugation test: Those formulations which passed the heating cooling cycle test then subjected to centrifugation test at 3500 rpm for 30 min. Those formulations that did not show any sign of phase separations, which are most thermodynamically stable.[22]

Dispersibility test

The efficiency of self-micro emulsifying drug delivery system was evaluated by the dispersibility test. Dipersibility study was performed by adding each formulation in 500 ml of distilled water at 37˚C ± 0.5˚C. A standard stainless steel dissolution paddle rotating at 50 rpm provided gentle agitation. The in vitro performance of the formulation was visually evaluated using the following grading system.

- **Grade A:** Rapidly forming emulsion having a clear or bluish appearance (within 1 min)
- **Grade B:** Rapidly forming slightly less clear emulsion, having a bluish white appearance.
- **Grade C:** Fine milky emulsion was formed (Within 2 min).
- **Grade D:** Dull, grayish white emulsion having slightly oily appearance (Longer than 2 min).
- **Grade E:** Formula exhibiting either poor or minimal emulsification with large oil globules present on the surface.[16]

Self emulsification time

A standard USP dissolution apparatus type II was used to test the self-emulsification efficiency of SEDDS. In 900 ml of 0.1N HCI kept at 37 °C, a quantity equivalent to 25mg of each formula's microemulsion was added. A typical stainless steel dissolving paddle moving at 75 rpm provides agitation. The rate of emulsification and final appearance of the microemulsion were visually analysed for the created formulae. These investigations were carried out in order to better replicate the state of the stomach following oral ingestion. With respect to time, the tendency to emulsify spontaneously and the progression of emulsion droplets were observed.[23]

Globules size measurement and PDI

In a beaker, SEDDS formulation (1 ml) was diluted with 100 ml deionized water and constantly stirred with a glass rod. The microemulsion that resulted was then tested for globule size and PDI. Dynamic light scattering with particle size apparatus was used to determine the globule size and PDI of the resulting micrommalsion (Malvern Zetasizer, Ver. 7.12, serial Number: MAL 1098084, UK). The particle (droplet) size was measured at equilibrium. The lowest droplet size values that are more stable, isotropic, and transparent oil/water (o/w) dispersions that have a higher absorption rate potential.[24]

Zeta potential

Zeta potential is the electric potential in the interfacial double layer. Zeta potential is a key indicator of stability. It is indicating the electrostatic repulsion and congregation in oily droplets. The electrostatic repulsion of emulsion droplets plays an important role for assessment of stability of the system High electrostatic repulsion droplets prevent coagulation or flocculation on to fine emulsion droplets into larger oily globules.[25] Zeta potential determined by Zetasizer was monitored at 25°C at a scattering angle 173 (Malvern Zetasizer. Ver. 7.12, serial Number: MAL 1098084. UK)

% Transmittance

The percent clarity of the prepared samples was assessed to demonstrate the formulation's transparency. Using a UV-spectrophotometer and distilled water as a blank, the % transmittance of the system is determined at 650 nm wavelength. If the percent transmittance of a formulation is greater than 99 percent, the formulation is transparent.[21]

Drug content

The drug content was determined by dissolving SEDDS formulation equivalent to 10 mg drug in 50 ml of methanol and mixed well with shaking for two to three times 0.1 ml of this solution was diluted with fresh methanol, and drug content was determined spectrophotometrically (Shimadza 1800, Japan) at 233nm.[26]

Preparation of solid sedds

By using an adsorption approach, liquid SEDDS were turned into free-flowing powders, resulting in a more uniform drug release profile. Drops of liquid SEDDS were added to aerosil 200 in 1:0.25, 1:0.5, 1:1, 1:1.5, and 1:2 ratios, and the mixture was stirred for 5 minutes in a mortar pestle. To ensure a consistent dispersion of the formulation, the mixture

was homogenised with a glass rod after each addition. The final mass was passed through mesh no. 120 (0.125mm), dried at room temperature, and stored in desiccators until further examination.[16,27]

Evaluation of solid sedds

Flow properties

Bulk density, tapped density, Hausner's ratio, Carr's index, angle of repose was evaluated.

Reconstitution properties of solid SEDDS

Effect of dilution on solid SEDDS

The property of quick emulsification was noticed after 100 mg S-SEDDS was correctly weighed and added to 100 ml distilled water in a beaker at 37°C and gently stirred with a magnetic stirrer at 100 rpm. The tendency to produce an emulsion was determined as follows:

- Good - If emulsification occurs in <1 min with clear or transparent emulsion.
- Bad – If emulsion if less clear or transparent[16]

In vitro dissolution test

The drug dissolution profile was studied using the USP dissolution apparatus II (Electrolab, Mumbai). Dissolution tests were performed in 900 ml of 0.01 N HCI (pH 2.0) at 37 0.5 °C with 75 rpm stirring. 10 mg of LP and formulation batches were introduced to the dissolution medium, and 5 ml samples were withdrawn after 10, 20, 30, 40, 50, and 60 minutes, and replaced with 5 ml fresh 0.5 percent Polysorbate 20 in 0.01 N HCL each time. The solutions were immediately filtered through a 0.45 um membrane filter, diluted, and UV-spectrophotometrically measured at 233nm.[28]

Drug and excipient interaction

ATR-FTIR spectra of pure LP, Aerosil 200, physical mixtires and Solid SEDDS formulations were recorded by ATR-FTIR Spectrometer (ALPHA 100508 BRUKER. US) to illustrate the promising interactions among the excipients used in the formulation. The spectrum was scanned over the wave number range of 4000-400 cm^{-1}[16]

RESULT AND DISCUSSION

% Practical yield

% Practical yield of synthesized surfactant was found to be 84.32%.

Melting point

Melting point of synthesized surfactant was found to be 135˚C

Fourier transforms infrared (FTIR) spectroscopy

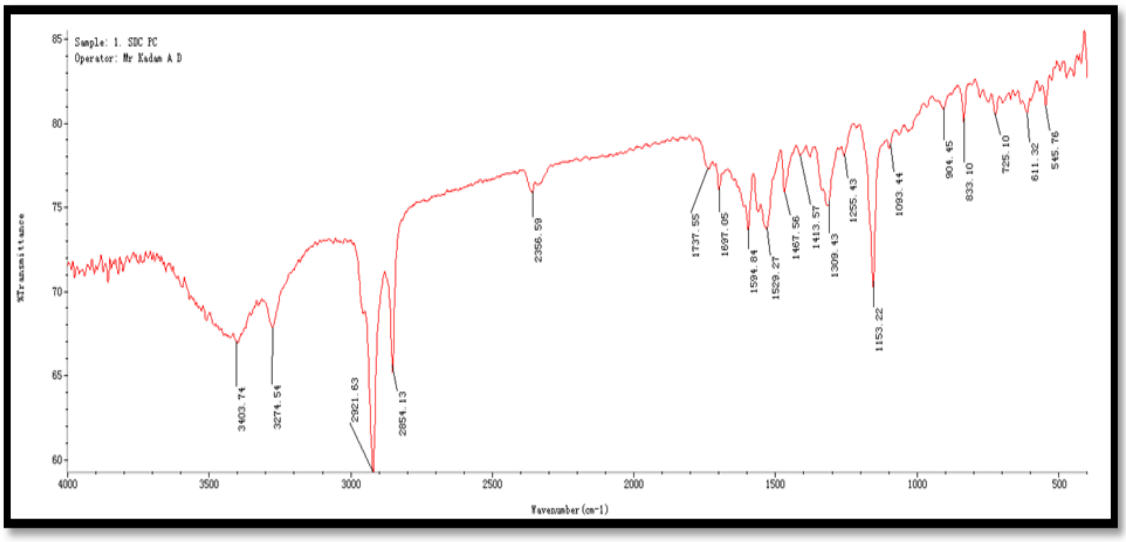

Fig. 1: ATR-FTIR spectrum of SDC-PC.

ATR-FRIR spectrum of SDC-PC is given in above figure. The spectrum shows NH_2 asymmetric at 3403.74 cm^{-1}, NH at 3274.54 cm^{-1}, CH_2 asymmetric at 2921.63 cm^{-1}, CH_2 symmetric at 2854.13 cm^{-1}, C=C aromatic at 1529.27 cm^{-1}, C-N at 1309.43 cm^{-1}, C-S at 1153.22 cm^{-1}. All characteristic peak of surfactant found in reported range.

Critical micelles concentration

The critical micelles concentration is an important phenomenon for scientist and researchers in the field of drug delivery. The micellization is the property of non ionic surfactant and polymers. No-ionic surfactant when exposed to the water forms aggregations called as micelles. When surfactants are added to a solvent, they are dispersed in the solution. By increasing the concentration of surfactant i the medium, at CMC they form micelles. CMC can be found by plotting graph of suitable physical property as a function of surfactant concentration. The CMC values of synthesized surfactant were determined by plotting the absorbance at λ_{max} against the concentration of each surfactant. The surfactant SDC-PC was read ranging from 0.01-0.1 µg/ml concentration and its CMC was calculated as 0.06mM.

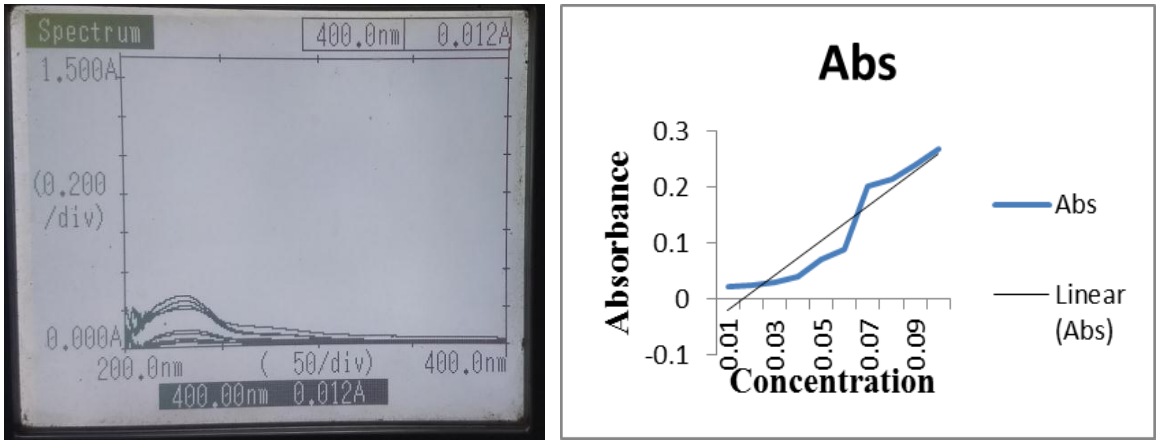

Fig 2: UV-visible spectra and CMC of SDC-PC.

Solubility study

After performing solubility study, the drug was found to be more soluble in oleic acid (oil), SDC-PC (surfactant), PEG400 (co-surfactant) results are shown in fig.

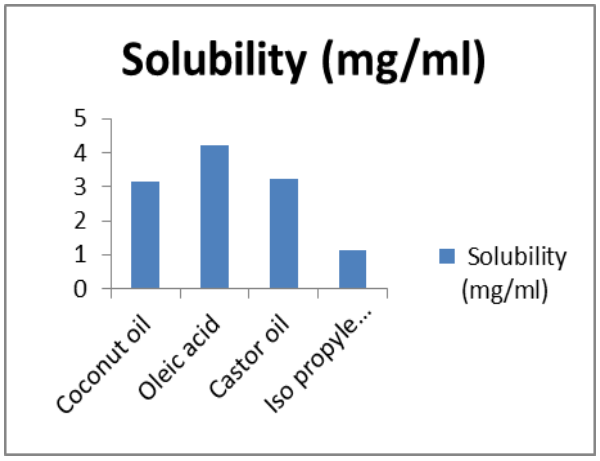

Fig. 3: solubility in various oils.

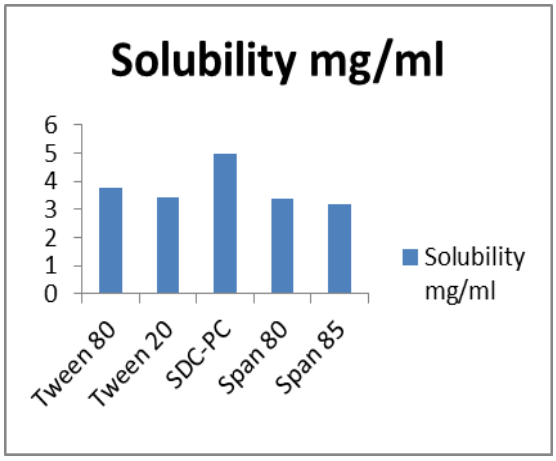

Fig. 4: Solubility in various surfactant.

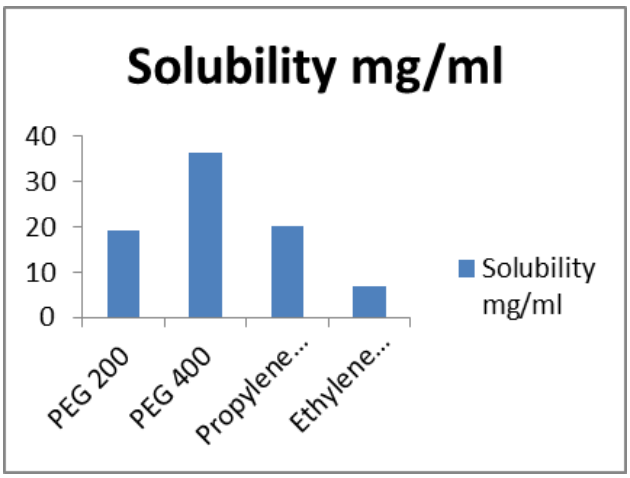

Fig. 5: Solubility in various co-surfactant.

Construction of ternary phase diagram

The pseudo-ternary phase diagram is useful to determine the suitable combination of oil, surfactant and co-surfactant concentration in the formulation to form the nano-emulsion. After selection of oil, surfactant and co-surfactant based on the solubility study, the pseudo-ternary phase diagrams containing a fixed ratio of surfactant and co-surfactant (Smix) were constructed. The ternary phase diagram of the system containing SDC-PC: PEG 400 with the ratio of 1:9 formed with the wider emulsifying region in the presence of oleic acid as oil. It is clear from Fig.7 that the emulsifying region increases with an increase in the amount of surfactant mixture concentration in the system. Several reports explained this phenomenon of a decrease in the mean droplet size as an outcome of an increase in the concentration of surfactant and vice versa. The reduced droplet size with a high concentration of surfactant mechanism may be supported with the following statements:

- Stabilization of the oil droplet occurs with reduction in the interfacial tension between oil and water phase at a high concentration of surfactant.
- Enhancement of water penetration into oil in the presence of high surfactant which causes the release of oil droplets in aqueous phase

The addition of the drug did not affect the self-emulsifying region significantly.

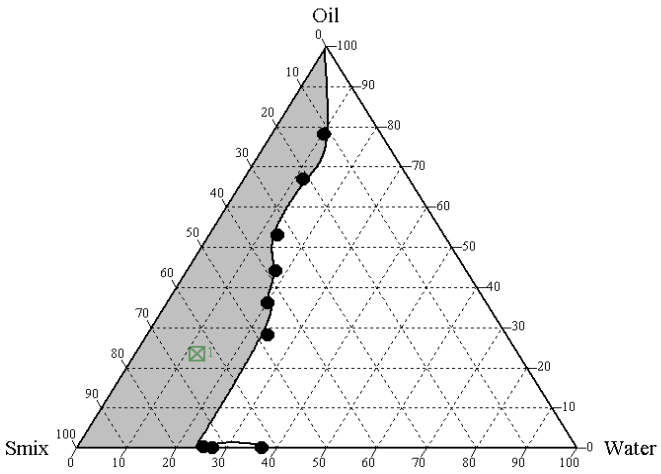

Fig. 7: Ternary phase diagram (Smix 1:9).

Preparation of liquid SEDDS

A total of four (4) formulations LP1 to LP4 were successfully prepared with their respective composition as shown in table 1.

Table 1: Formulation table of Liquid SEDDS.

Batch code	Drug (mg)	Oil (%)	$Smix_1$ (%)	$Smix_2$ (%)	Weight of batch (%)
LP1	25	70	-	30	100
LP2	25	60	-	40	100
LP3	25	50	-	50	100
LP4	25	40	-	60	100

Thermodynamic stability study

The thermodynamic studies have always helped determine the kinetic stability of the formulation. The main criteria of microemulsion for pass this test is not to show any indication of phase separation, creaming, cracking or coalescence. All the prepared formulations had passed the thermodynamic study test, with no signs of phase separation and precipitation of drugs. This indicates that the prepared formulations were stable against the maintained storage conditions.

Dispersibility test

The dispersibility of microemulsion shows Grade A of all formulations showed a rapidly forming emulsion having a clear or bluish appearance (within 1 min).

Table 2: Dispersibility grades and self emulsification time.

Sr. No.	Batch	Dispersibility Grade	Self emulsification time (sec)
1	LP1	A	54
2	LP2	A	48
3	LP3	A	45
4	LP4	A	44

Self emusification time study

The emulsification time of all batches was found to be in the range of 44 to 54 seconds as shown in Table 2. The batch LP4 showed very short emulsification time. The determination of self emification time for the assesment of microemulsion spread or scatters in GIT medium. Smaller the size of particle faster the lease and shows the efficiency of formulation.

Globule size, PDI and Zeta potential

Globule size of emulsion plays important role in absorption and also in stability. Globule size of optimized formulation was observed 836.7 nm (Fig.8) which is within the range of nano-emulsion (500-1000nm) and polydispersity index (PDI) was observed 0.466. Zeta potential of

optimized batch was observed -0.329 mV (Fig.9) negative potential around particles shows improved lymphatic uptake of system.

Table No.: Globule size, PDI and zeta potential of all batches.

Batch	Globule size	PDI	Zeta potential
LP1	583.8	0.975	0.527
LP2	1671	0.040	0.0608
LP3	974.6	0.604	-0.0518
LP4	836.7	0.466	-0.329

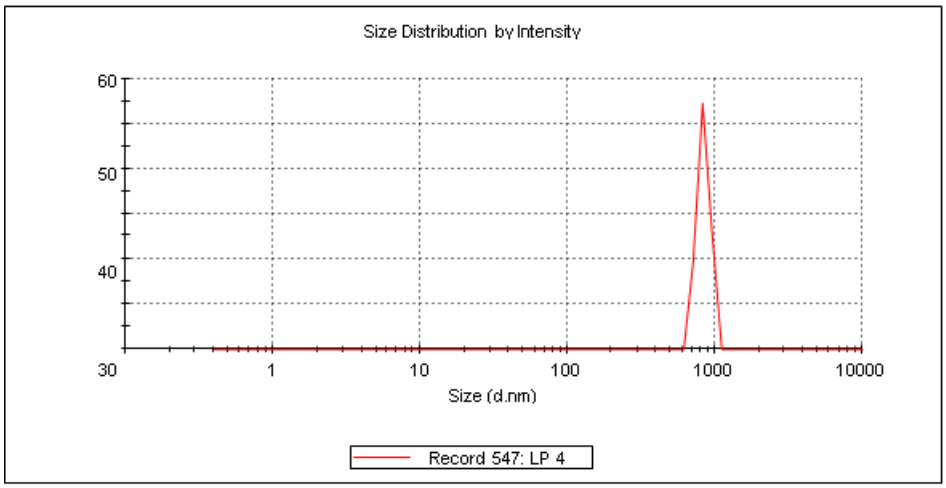

Fig. 8: Globule size distribution graph of optimized batch.

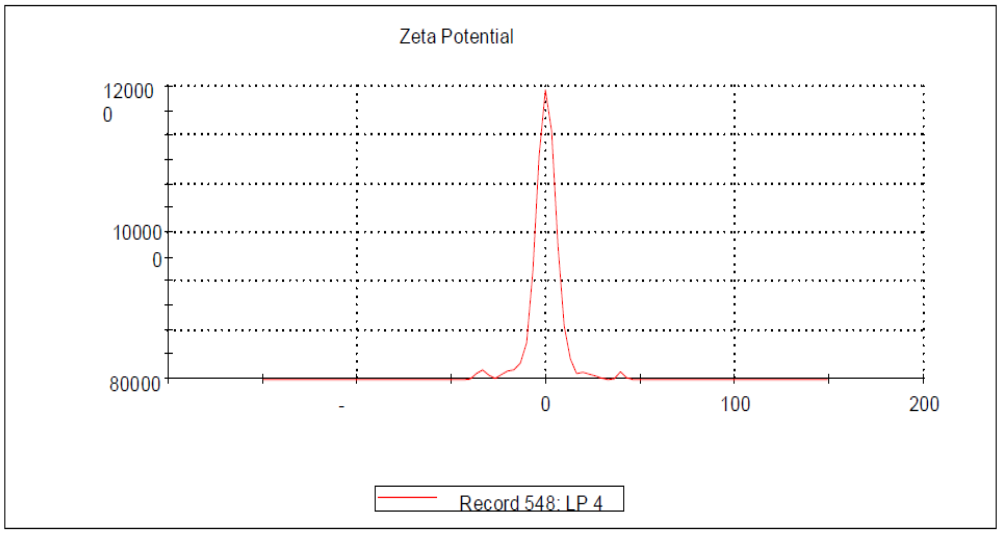

Fig. 9: Zeta potential of optimized batch.

% Transmittance measurement

Percent transmittance was evaluated for proving the transparency of formulation. A value closer to 100% confirms, the transparency of the formulation and indicates large surface area

for drug release. Percent transmittance of formulation was found to be in the range of 100% to 93.2 % and tabulated in Table 3.

Table 3: % transmittance measurement.

Sr. No.	Batch	% Transmittance
1	LP1	96.1
2	LP2	98.3
3	LP3	99.0
4	LP4	100.3

Drug content

The drug content of the prepared losartan potassium loaded SEDDS was determined to evaluate the uniformity of dose in the formulation. The drug content in different prepared batches is listed in table 29. Drug content of liquid SEDDS formulation batch LP4 was found to be highest as 98.81%. So it was considered as obtimized batch for further evaluation.

Table 4: Drug content of liquid SEDDS formulation.

Sr. No.	Batch	Drug content (%)
1	LP1	98.32
2	LP2	97.56
3	LP3	98.79
4	LP4	98.81

Formulation of solid SEDDS

From the evaluation of liquid SEDDS it was observed that LP4 was optimized batch so LP1, LP2, LP3, LPV4 batches are converted to solid SEDDS to avoid stability problems. Solid SEDDS formulations were prepared by using the carrier i.e. Aerosil 200. Optimized liquid SEDDS converted into solid SEDDS by using adsorption technique. The solid carrier demonstrated to be effective to construct free flowing powder form of liquid SEDDS with high surface area. The amount of carrier required to absorb the liquid SEDDS was strongly associated with the surface area of adsorbant.

Table 6: Formulation batches of solid SEDDS.

Batch code	Liquid SEDDS (mg)	Aerosil 200 (mg)	Total wt. of tablet (mg)
LP1	350	250	600
LP2	350	250	600
LP3	350	250	600
LP4	350	250	600

*Calculation for one dose; batch size 20 tablets

Evaluation of Solid self emulsifying drug delivery

Flow properties

Flow properties of solid SEDDS such as angle of repose, bulk density, tapped density, carr's index and hausner's ratio are deteremined and found that the prepared solid SEDDS showed "Good" flow properties as showed in Table 7.

Table 7: Flow properties of Solid SEDDS.

Batch	Bulk density (gm/ml)	Tapped density (gm/ml)	Hausner's ratio	Carr's index	Angle of repose
LP1	0.77	0.75	1.1	9.09	27.75
LP2	0.81	0.76	1.06	15.71	29.05
LP3	0.76	0.65	1.26	7.89	27.14
LP4	0.81	0.70	1.09	13.58	26.56

Effect of dilution on solid SEDDS

The formulation LP4 has found to have "Good" dilution than that of other formulations.

In-vitro dissolution test

In-vitro drug released was performed between marketed formulation and optimized batches. The in-vitro dissolution of prepared solid SEDDS was compared with marketed formulation (LOSAR®). From the result it was observed that LP4 shows more release compared to the marketed formulation these findings conclude an enhancement of permeability and, as a result the improved bioavailability of Losartan potassium.

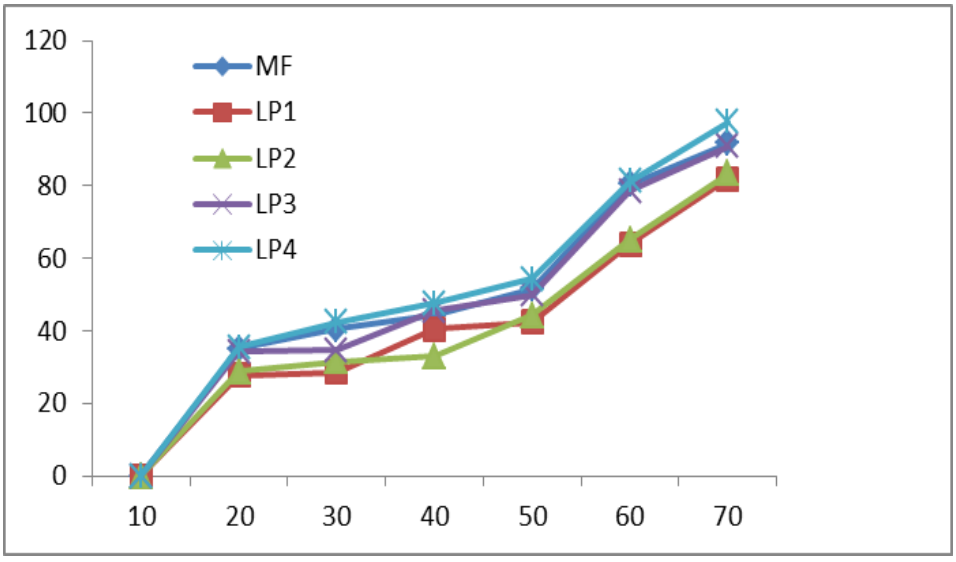

Fig. 11: In-vitro drug release.

Drug excipient interaction by ATR-FTIR

From the observation of all FTIR spectra, it was evident that all important peak of losartan potassium and the excipients used were located in the solid SEDDS. Hence it could be concluded that there was not any chemical interaction between the drug and excipients.

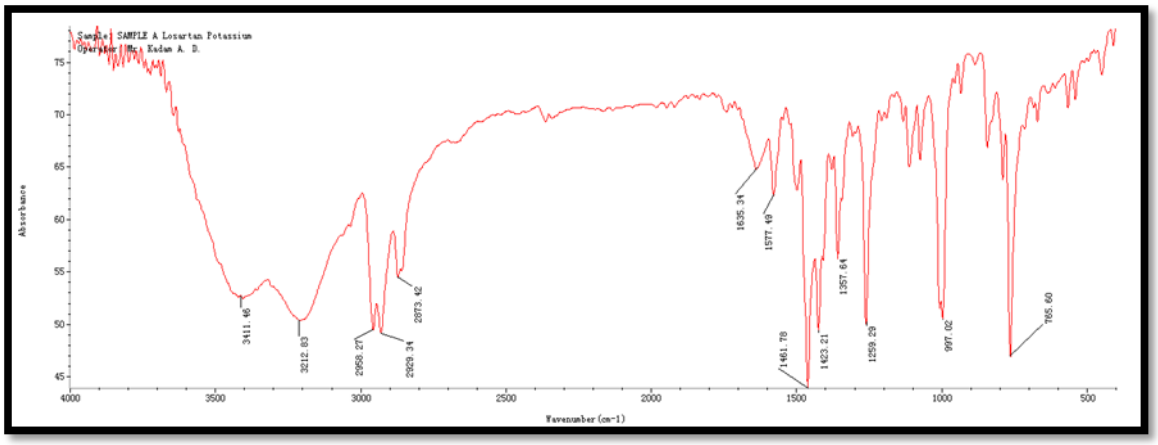

Fig. 12: Infrared spectrum of Losartan potassium.

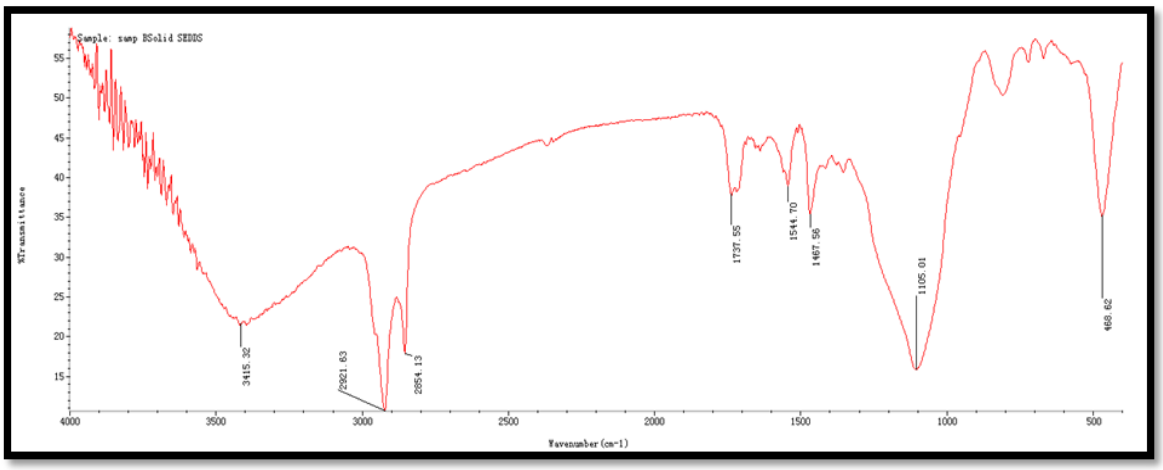

Fig 13: Infrared spectrum of solid self emulsified drug delivery system.

CONCLUSION

Liquid SEDDS of losartan potassium with oleic acid as oil phase, SDC-PC as surfactant and PEG400 as co-surfactant was successfully developed. Based on thermodynamic stability study, self emulsification time, % transmittance, zeta potential, particle size study LP4 formulation was selected. Based on above studies it was concluded that SDC-PC can be used as surfactant in SEDDS which shows good results. So LP4 formulation further converted to solid SEDDS using Aerosil 200 as a carrier and evaluated for the flow properties, effect of dilution, in-vitro drug release and FTIR studies. % drug release of solid SEDDS was almost similar to marketed formulation LOSAR®.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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