

Original Article

FORMULATION AND CHARACTERIZATION OF LOSARTAN LOADED SELF EMULSIFYING DRUG DELIVERY SYSTEM

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ABSTRACT

Objective: The object of the present work was the advancement and portrayal of losartan stacked self-emulsifying drug conveyance framework for the successful administration of hypolipidemia (RSEDDS) for further developing bioavailability, to upgrade dissolvability, delays home time, give an adequate measure of medication to an objective site and supported the arrival of medication.

Methods: Self-Emulsifying Drug Delivery System was ready by the basic emulsification method. Six clumps, for example, F1 to F6 were ready by shifting the convergence of oils, surfactant, co-surfactant, and co-dissolvable and assessed for the different boundaries, for example, Optical microscopy, Assessment of self emulsification, Emulsification time, Droplet size investigation, Zeta Potential Measurement, Transmission Electron Microscopy, Viscosity Determination, Drug content, Percentage conveyance, *in vitro* disintegration study and solidness study. The SEDDS was upgraded and group F5 was additionally utilized.

Results: The medication content of chosen clump F5 was viewed as 97.65 ± 1.37 %; it proposes that the technique for exemplification was powerful. As per *in vitro* study, around 55.13 % of the medication was delivered after 120 min which showed supported arrival of medication and there were no critical changes seen in the actual appearance, drug content, and *in vitro* drug release during the stability study.

Conclusion: This research presumed that the SEDDS are an expected competitor as a supported delivery drug conveyance, effectively expanding bioavailability and designated conveyance of medication.

Keywords: Self-emulsifying drug delivery system, Losartan, Sustained-release, TEM, *In vitro* release

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INTRODUCTION

Traditional medication conveyance framework just a small part of portion ranges to fundamental blood dissemination and henceforth the majority of the portion is squandered and cause unwanted aftereffects and poisonousness and furthermore the ordinary dose structures are impacted by the gastric climate, pH conditions, and response with the stomach dividers, GI motility and presence of food in the GI parcel. Because of this, the medication discharge design from measurement structure is impacted, which thus influence the helpful example. This outcome in longer time of dosing, patient burden and other fundamental impacts [1]. The oral route is the most popular route among all the route of administration. Approximately 40% of new drug candidates have poor water solubility and the oral delivery of such drugs is frequently associated with low bioavailability, high intra-and inter-subject variability, and a lack of dose proportionality [2]. Recently much attention has been paid to lipid-based formulations with particular emphasis on self-emulsifying drug delivery system (SEDDS), to improve the oral bioavailability of lipophilic drugs [3].

Self-emulsifying drug conveyance framework (SEDDSs) has acquired openness for their capacity to build dissolvability and bioavailability of inadequately solvent medications. SEDDSs are isotropic combinations of oils and surfactants; now and again it contains co-solvents and it tends to be utilized for the plan of details to work on the oral retention of exceptionally lipophilic compounds. SEDDS emulsify suddenly to create fine oil-in-water emulsions when brought into a fluid stage under delicate fomentation. SEDDS can be directed orally in delicate or hard gelatin cases and structure fine, moderately stable oil-in-water emulsions upon fluid weakening [4]. Expected benefits of these frameworks incorporate upgraded oral bioavailability, more steady transient profiles of medication assimilation, particular medication focusing toward a particular retention window in the GI lot, and medication assurance from the antagonistic climate in the stomach.

Losartan is a cholesterol-bringing specialist generally utilized down to treat hypercholesterolemia. Losartan is a glasslike powder with a liquefying point of 151-156 °C that is sparingly dissolvable in water and ineffectively retained from the gastro-digestive system. After oral organization alone, Losartan is quickly assimilated most extreme plasma focuses in under 3 h. Degree of assimilation expansions with respect to the Losartan portion. The outright bioavailability of Losartan (parent drug) is around 20% and the fundamental accessibility of HMG-CoA reductase inhibitory action is roughly 30%. Oral bioavailability is the most serious issue of Losartan calcium as it is somewhat water dissolvable.

In view of these contemplations, the destinations of this paper were to create losartan stacked self-emulsifying drug conveyance framework for the compelling administration of hypolipidemia (RSEDDS) to upgrade the solvency and further developing bioavailability of SEDDS of Losartan and to manage them through oral course bringing about expanding their clinical viability.

MATERIALS AND METHODS

Losartan was kindly provided as a gift sample by Medley Lab, Jammu, India.

Preparation of Self emulsifying drug delivery system. This involved mixing of different oils, surfactant, co-surfactant and co-solvent shown in table [1].

First weighed amount of Losartan was broken down in ethanol by constant blending in a container until it completely disintegrated. Then, at that point, a measure of oleic acid was added gradually with nonstop mixing into the drug-ethanol blend. In another beaker fitting measure of PEG-400 was added to Tween-80 and blended appropriately by ceaseless mixing with a glass pole. After nonstop

blending, the combination of Tween-80 and PEG-400 was added to the medication ethanol blend by attractive mixing at 100 rpm for 30

min. The detailing of SEDDS was put away in a very much shut compartment for its further portrayal [5].

Table 1: Formulation of SEDDS

Formulations	Drug (Losartan) in mg	Tween-80 in ml	PEG-400 in ml	Ethanol in ml	Oleic acid in ml	Glycerin in ml
F1	50	3.7	-	3.6	3.7	4
F2	30	3.7	4.0	3.6	3.7	-
F3	50	3	-	4.5	3.6	4.5
F4	30	3	4.5	4.5	3.6	-
F5	50	5	2.5	2.5	5	-
F6	30	5	-	2.5	5	2.5

Selection criteria for preparation of (F5) formulation

The selection of formulation F5 was done on the basis of self-emulsification assessment; when compared to other formulations; the F5 formulation formed a rapidly forming emulsion having a clear or bluish appearance i.e. the formulation F5 was of Grade-A preparation (table 2). In the above formulation design the F5 formulation is selected for further study and characterized for various parameters [6].

Table 2: Assessment of self emulsification for various SEDDS formulations

Formulation	Grade
F1	C
F2	B
F3	D
F4	C
F5	A
F6	B

Grade A: Rapidly forming emulsion having a clear or bluish appearance.

Grade B: Rapidly forming, slightly less clear emulsion, having a bluish-white appearance.

Grade C: Fine milky emulsion that formed within 2 min.

Grade D: Dull, grayish-white emulsion having the slightly oily appearance that is slow to emulsify longer than 2 min.

Grade E: Formulation, exhibiting either poor or minimal emulsification with large oil globules present on the surface [7].

Characterization of formulation (F5)

The opted formulation (F5) was selected and characterized for various parameters like optical microscopy, Assessment of self emulsification, Emulsification time, Droplet size analysis, Zeta Potential Measurement, Transmission Electron Microscopy, Viscosity Determination, Drug content, Percentage transmittance, *in vitro* dissolution study and stability study.

Optical microscopy

The opted formulation (F5) of SEDDS observed under an optical microscope (fig. 1)

Assessment of self emulsification

The efficiency of self emulsification was assessed using standard US pharmacopoeia XXIII dissolution apparatus type II. One gm of formulation was added dropwise to 200 ml of at 37 °C. Gentle agitation was provided by a standard stainless steel dissolution paddle at 60 rpm. The *in vitro* performance of the formulation was visually assessed using the following grading system (table 3) [8, 9].

Grade A: Rapidly forming emulsion having a clear or bluish appearance.

Grade B: Rapidly forming, slightly less clear emulsion, having a bluish-white appearance.

Grade C: Fine milky emulsion that formed within 2 min.

Grade D: Dull, grayish-white emulsion having the slightly oily appearance that is slow to emulsify longer than 2 min.

Grade E: Formulation, exhibiting either poor or minimal emulsification with large oil globules present on the surface.

Emulsification time

The emulsification time of SEDDS was determined according to USP XXIII, dissolution apparatus II. 0.5 g of the SEDDS formulation (F5) was introduced into 250 ml of 0.1N HCl in 500 ml conical flask under the action of magnetic stirrer (Jaico) rotating at a constant speed (50 rpm) and emulsification time was noted (table 4) [10]

Droplet size analysis

Droplet size determines the rate and extent of drug release as well as the stability of the emulsion. Formation of SEDDS, which are stable, isotropic and clear o/w dispersions, takes place on reduction of the globule size. SEDDS formulation (F5) was diluted to 100 ml with distilled water in a flask and is mixed gently by inverting the flask. The droplet size was determined by dynamic light scattering (DLS) technique using Zetasizer (Zetasizer Ver. 6.01, Malvern Instruments, UK) (table 5) [11]

Zeta potential measurement

The emulsion stability is directly related to the magnitude of the surface charge. The magnitude of the zeta potential gives an indication of the potential stability of the colloidal system. If all the particles have a large negative or positive zeta potential, they will repel each other and there is dispersion stability. The zeta potential of the diluted SEDDS formulation was measured using a (Malvern Zetasizer 3000HS). The SEDDS were diluted with a ratio of 1:20 v/v with distilled water and mixed for 1 min using a magnetic stirrer and recorded the result (table 6) (fig. 2) [12, 13].

Transmission electron microscopy

SEDDS formulation F5 was diluted with distilled water 1:30 and mixed by gentle shaking. Copper grids are allowed to stand on for 60 seconds, on which one drop of the sample is obtained after dilution was deposited. Filter paper is used to remove excess fluid and then the grid was stained in 1% phosphotungstic acid solution for 30 seconds. By following, method TEM of RSEDDS was provided (fig. 3) [14, 15].

Viscosity determination

Viscosity study is necessary for SEDDS to characterize the system physically and to control its stability. The viscosity of the Losartan SEDDS is crucial in determining its ability to be filled in hard or soft gelatin capsules. If the system has very low viscosity, it may enhance the probability of leakage from the capsule and the system with very high viscosity may create problems in pourability.

SEDDS of Losartan (1 ml) was diluted with the distilled water in a beaker with constant stirring on the magnetic stirrer. Viscosity of the resultant emulsion and initial SEDDS was measured using Brookfield viscometer (DV-III ultra Brookfield). The data of viscosity of SEDDS formulation F5 was recorded (table 7) [16, 17]

Drug content

The drug content of Losartan SEDDS formulation was measured using UV spectroscopic method. The drug content uniformity was determined by preparing 10 µg/ml of aliquot of SEDDS sample using methanol as solvent. The samples were suitably diluted and the absorbance of the solutions was measured at 240 nm using a UV-Visible spectrophotometer (EI double beam spectrophotometer 1372 UV-Spectrophotometer) against methanol as a blank. The amount of Losartan was estimated by using standard calibration curve of the drug. The data of percent drug content in SEDDS formulation (F5) was recorded in the table (table 8) [18].

Percentage transmittance

Percent transmittance proved the transparency of formulation. The percent transmittance of the system is measured at a particular wavelength using UV spectrophotometer (EI double beam UV-VIS spectrophotometer UV/Visible model 1372) by using distilled water as blank [19, 20]

A total of 1 ml SEDDS formulation was diluted 100 times with distilled water. Percentage of transmittance was measured spectrophotometrically (EI double beam spectrophotometer 1372 UV Spectrophotometer) at 560 nm using water as a blank (table 9).

In vitro dissolution study

The quantitative *in vitro* drug discharge from detailing was contemplated to survey in the event that self-emulsifying properties stay reliable. The USP XXII, disintegration contraption (Electrolab TDT-06I) was used to concentrate on the arrival of the medication from the oil in the watery framework. Hard gelatin case containing SEDDS was attached to oar to keep the container from drifting 900 ml disintegration media were utilized standard phosphate cushion arrangement pH 7.4.

To think about various SEDDS, disintegration studies were done at 37±0.5 °C, utilizing paddle pivoting at 75 rpm, 1 ml example was removed at 30, 60, 90, 120, 150, 180 min. The example volume of new media replaces the removed example. The test was channeled through Whatman filter paper and investigated spectrophotometrically (EI twofold shaft UV-VIS spectrophotometer UV/Visible model 1372) at 240 nm. The medication discharge from the SEDDS detailing was viewed as fundamentally higher as contrasted and that of pure drug and marketed preparation (table 10) (fig. 4) [21].

Stability studies

The optimized formulations (F5), which was selected for stability testing under storage condition at 4±1 °C, at 25±2 °C (room temperature) and at 40±1 °C (Thermostatic oven). Formulation (F5) was stored in screw-capped, amber-colored small glass bottles at 4±1 °C, room temperature (25±2 °C) and 40±1 °C. Analysis of the sample was made for % drug content after a period of 15, 30, 45 and 60 d. Subsequent change in % Drug content of the formulations stored at 4±1 °C, at room temperature 25±2 °C and at 40±1 °C (Thermostatic oven) was determined after a definite period of time of 15, 30, 45, and 60 d (table 11, 12 and 13 and fig. 5, 6 and 7) [22]

Table 2: Assessment of self emulsification for various SEDDS formulations

Formulation	Grade
F1	C
F2	B
F3	D
F4	C
F5	A
F6	B

RESULTS

The selection of formulation F5 was done on the basis of self emulsification assessment; when compared to other formulations;

the F5 formulation formed a rapidly forming emulsion having a clear or bluish appearance that is the formulation was of Grade-A preparation. In the above formulation design, the F5 formulation is finalized for further study that is used for characterization under various parameters (table 2 and 3). The self emulsification assessment of SEDDS showed that the preparation was of Grade A that is a rapidly forming emulsion having a clear or bluish appearance. It was observed that an increase in the proportion of oil in the formulation resulted in decreasing self-emulsification time.

Table 3: Assessment of emulsification grade (F5)

Formulation code	Parameter	Observation
F5	Assessment of self emulsification	Grade A

Grade A: Rapidly forming emulsion having a clear or bluish appearance.

Grade B: Rapidly forming, slightly less clear emulsion, having a bluish-white appearance.

Grade C: Fine milky emulsion that formed within 2 min.

Grade D: Dull, grayish-white emulsion having the slightly oily appearance that is slow to emulsify longer than 2 min.

Grade E: Formulation, exhibiting either poor or minimal emulsification with large oil globules present on the surface.

The opted formulation (F5) of SEDDS was observed under an optical microscope (Labmed) and it was found that the developed formulation contained the droplets in emulsion (fig. 1).

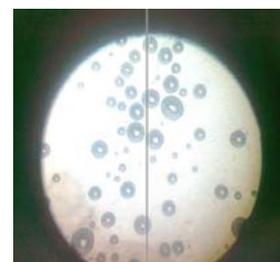


Fig. 1: Photograph of formulation (F5) of SEDDS of Losartan under an optical microscope

The emulsification time of SEDDS was 19±5.51 seconds which resulted in a good tendency for emulsification (table 4).

Table 4: Emulsification time of SEDDS formulation (F5)

Formulation code	Parameter	Result
F5	Emulsification time	19±5.51 Sec.

The droplet size of SEDDS (F5) formulation was found to be 125.89 nm which explained that the smaller droplet size presents large surface area for drug absorption (table 5).

Table 5: Droplet size analysis of SEDDS formulation (F5)

Formulation code	Parameter	Result
F5	Droplet size	125.89 nm

The zeta potential value of SEDDS (F5) was found to be -25.7 mV negative charge indicates that the emulsion particles were stable (table 6) (fig. 2)

Table 6: Zeta potential of SEDDS formulation (F5)

Formulation code	Parameter	Result
F5	Zeta potential	-25.7 mV

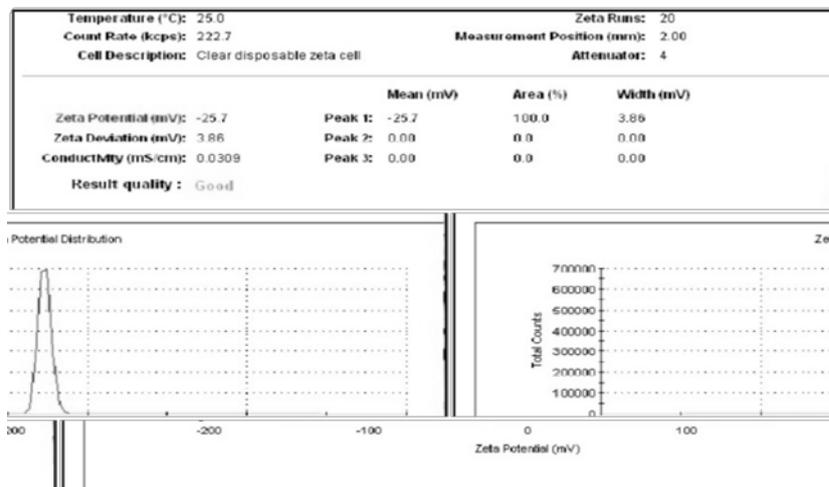


Fig. 2: Zeta potential of SEDDS formulation (F5)

The TEM photograph shows the surface morphology of the SEDDS (F5) as seen in fig. 3; the nanosized droplets as discrete particles can

be seen in the TEM analysis is evidence to show that the adsorption onto solid carrier was good as no oil droplets are visible.

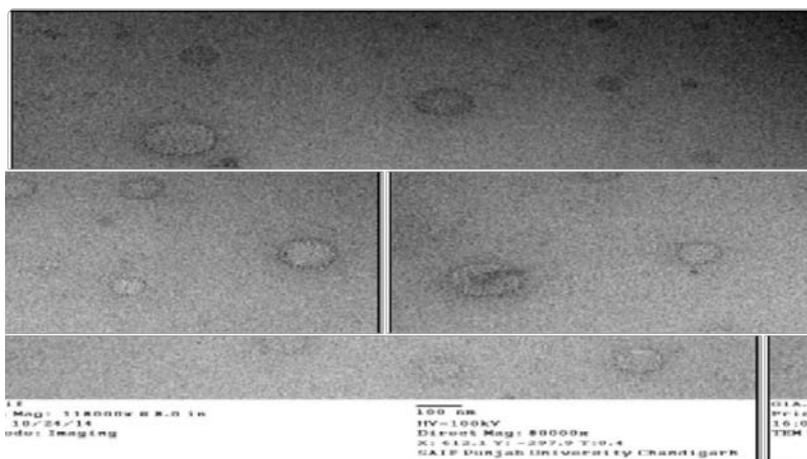


Fig. 3: TEM photograph of SEDDS of Losartan (F5)

Viscosity of SEDDS (F5) was found to be 12.2±0.2 (cP) Thus, it showed o/w emulsion where water remains as external phase and viscosity of SEDDS is near to water which indicated that Losartan emulsion on dilution with the fluid its viscosity getting decreased and thereby absorption will be faster (table 7).

Table 7: Viscosity of SEDDS formulation (F5)

Formulation code	Parameter	Result
F5	Viscosity	12.2±0.2 cP

The percentage drug content was found to be 97.65±1.37, which is maximum and thus resulted in maximum drug release (table 8)

Table 8: Drug content of SEDDS formulation (F5)

Formulation code	Parameter	Result
F5	% Drug Content	97.65±1.37

The result of percentage transmittance was shown 97.45±1.78 (table 9). This result indicated the high clarity of SEDDS. The greater the particle size, oil globules may reduce the transparency of microemulsion and thereby values of percentage transmittance.

Table 9: Percentage transmittance of SEDDS formulation (F5)

Formulation code	Parameter	Result
F5	Percentage transmittance	97.45±1.78

The formulation of SEDDS (F5) showed a greater extent of drug release that is in 90 min the drug released was 44.23% when compared to pure drug and marketed formulation. The results suggested the potential use of SEDDS for oral administration of Losartan (fig. 4).

Accelerated stability studies only serve as tool for formulation screening and stability issues related to shipping or storage at room temperature. The results of the stability samples withdrawn at the end of 15 d, 30 d, 45 d and 60 d are shown in table (10, 11 and 12) at various temperature ranges. All the samples withdrawn at different time intervals formed clear dispersion and none of the formulations showed any drug precipitation and thus, the formulation was considered to be stable.

A progressive decrease in the emulsion % drug content has been observed in the samples withdrawn at different time intervals, which may be due to the aggregation of globules.

Losartan-loaded SEDDS (F5) was subjected to stability studies. The formulation was stored at 4±1 °C, at 25±2 °C (Room temperature)

and at 40 ± 1 °C (Thermostatic oven). From the results, it was found that % drug content had shown that formulation was more stable at 25 ± 2 °C rather than 4 ± 1 °C and 40 ± 1 °C (Thermostatic oven) storage

conditions. So it can be said that the formulation is more stable at 25 ± 2 °C for further use. Table (10, 11 and 12)

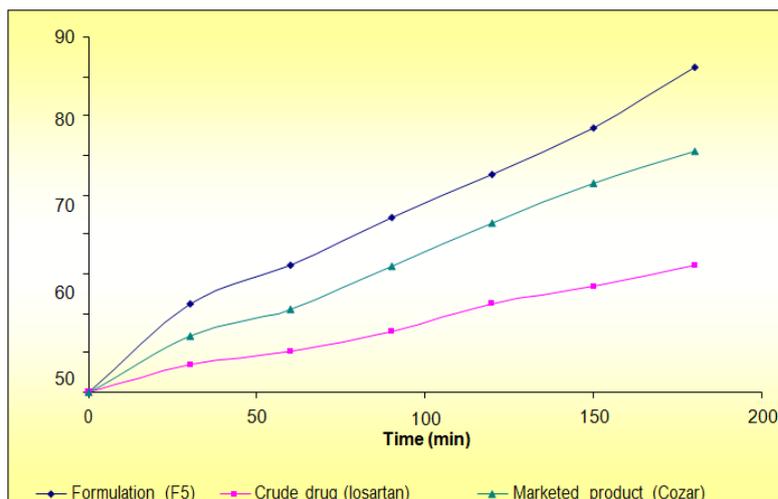


Fig. 4: Percentage drug release of F5, pure drug and marketed formulation

Table 10: Effect of storage on % drug content of SEDDS at 4 ± 1 °C

Formulation code	Time (days)	% Drug content At 4 ± 1 °C (refrigerator)
	0	97.6 \pm 1
F5	15	97.6 \pm 1
F5	30	97.3 \pm 1
	45	96.9 \pm 0.2
	60	96.5 \pm 0.6

Table 11: Effect of storage on % drug content of SEDDS at Room temperature (25 ± 2 °C)

Formulation code	Time (days)	% Drug content at room temperature (25 ± 2 °C)
	0	97.6 \pm 1
F5	15	97.4 \pm 1
F5	30	96.8 \pm 1
	45	96.1 \pm 0.3
	60	95.7 \pm 0.7

Table 12: Effect of storage on % drug content of SEDDS at thermostatic temperature (40 ± 1 °C)

Formulation code	Time (days)	% Drug content at thermostatic temperature (40 ± 1 °C)
	0	97.6 \pm 1
F5	15	97.1 \pm 1
F5	30	96.5 \pm 0.5
	45	95.8 \pm 0.9
	60	95.2 \pm 0.6

DISCUSSION

SEDDSs are isotropic combinations of oils and surfactants; now and then, it contains co-solvents and it very well may be utilized for the plan of definitions to work on the oral assimilation of profoundly lipophilic compounds.

Losartan is a hydrophobic and exceptionally porous medication which has a place with class II of biopharmaceutical arrangement framework (BCS). Low watery dissolvability of Losartan prompts high changeability in ingestion after oral organization. The current review was completed for the definition improvement of Losartan stacked self-emulsifying drug conveyance framework (SEDDS) with the point of upgrade its dissolvability as well as oral bioavailability. The SEDDS formulation was prepared using oil components (Oleic acid), surfactants (Tween 80), Co-surfactant (PEG-400) and Solvent

(Ethanol). Six formulations (F1, F2, F3, F4, F5 and F6) were developed with varying concentrations of oil, surfactant and co-surfactant by simple emulsification technique and preparation (table 1) F5 is selected for its further evaluation according to its good solubility parameters and assessment of self emulsification (table 2 and 3).

The self-emulsifying drug delivery system of Losartan was characterized for its Assessment of emulsification, Emulsification time, Droplet size analysis, Zeta potential measurement, Percentage transmission, Transmission Electron Microscopy, Viscosity Determination, Drug content, *In vitro* dissolution study and stability study.

The opted formulation (F5) of SEDDS was observed under an optical microscope (Labmed) and it was found that the developed formulation contained the droplets in emulsion (fig. 1).

The self emulsification assessment of SEDDS showed that the preparation was of Grade A that is a rapidly forming emulsion having a clear or bluish appearance (table 2 and 3). It was observed that an increase in the proportion of oil in the formulation resulted in decreasing self-emulsification time.

The emulsification time of SEDDS was 19 ± 5.51 seconds which resulted in a good tendency for emulsification (table 4). The droplet size of SEDDS (F5) formulation was found to be 125.89 nm which explained that the smaller droplet size presents large surface area for drug absorption (table 5). The zeta potential value of SEDDS (F5) was -25.7 mV negative charge indicates that the emulsion particles were stable (table 6) (fig. 2). The TEM photograph showed spherical surface morphology of SEDDS (F5) which resulted in higher drug loading (fig. 3). Viscosity of SEDDS (F5) was found to be 12.2 ± 0.2 , thus it showed o/w emulsion where water remains as external phase and viscosity of SEDDS is near to water which indicated that Losartan emulsion on dilution with the fluid its viscosity getting decreased and thereby absorption will be faster (table 7). The percentage drug content was found to be 97.65 ± 1.37 , which is the maximum and thus resulted in maximum drug release (table 8).

The result of percentage transmittance was shown 97.45 ± 1.78 (table 9). This result indicated the high clarity of SEDDS. The greater the particle size, oil globules may reduce the transparency of microemulsion and thereby values of percentage transmittance.

The formulation of SEDDS (F5) showed greater extent of drug release that is in 90 min the drug released was 44.23% when compared to pure drug and marketed formulation. The results suggested the potential use of SEDDS for oral administration of Losartan (fig. 4).

Losartan-loaded SEDDS (F5) was subjected to stability studies. The formulation was stored at 4 ± 1 °C, at 25 ± 2 °C (Room temperature) and at 40 ± 1 °C (Thermostatic oven). From the results, it was found that % drug content had shown that formulation was more stable at 25 ± 2 °C rather than 4 ± 1 °C and 40 ± 1 °C (Thermostatic oven) storage conditions. So it can be said that the formulation is more stable at 25 ± 2 °C for further use (table 10, 11 and 12).

CONCLUSION

Self-emulsifying plan of Losartan was effectively evolved. The oral bioavailability of inadequately water-solvent mixtures is expanded by utilizing this detailing framework. So in the future, the SEDDS might be utilized as an essential instrument in lessening the portion size in the plan. The current study showed effective readiness of self-emulsifying drug conveyance frameworks of Losartan.

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AUTHORS CONTRIBUTIONS

All authors have contributed in the studies performed and in the preparation of manuscripts.

CONFLICT OF INTERESTS

The authors report no conflicts of interest.

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