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Formulation and Characterization of Losartan loaded self emulsifying Drug Delivery System

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Abstract

In the current research work, losartan potassium (LP) loaded Self Emulsifying Drug Delivery System (SEDDS) was formulated using various ratios of lipids, surfactants and co-surfactants to prevent its first pass metabolism. A pseudo-ternary phase diagram was plotted to establish the emulsification region. Total of eight batches (F1 to F8) were prepared and subjected to different characterizations (thermodynamic study, phase separation, zeta potential and particle size) studies to obtain the optimized formulation. The optimized SEDDS (F8) with 40% oil, 60% surfactant and co-surfactant mixture (Smix) (6:1 ratio) was found to be a thermodynamically stable emulsion, with droplet size at around 204.7±5.0 nm, surface charge -13.38±1.5 mV and polydispersity index 0.221±0.03. The SEM study confirmed the spherical shape and even surface of the droplets. The In-vitro drug release profile of optimized formulation exhibited a similar rate and extent of dissolution as compared to the marketed formulation. Further, the optimized formulation had shown equivalent therapeutic efficacy (anti-hypertensive) with respect to the marketed tablet at half of the dose of the drug in SEDDS formulation.

Key words: Losartan, Self Emulsifying, Drug Delivery System, anti-hypertensive, lipids, surfactants, co-surfactants

Introduction

In recent years, the formulation of poorly soluble compounds presented interesting challenges for formulation scientists in the pharmaceutical industry. Up to 40% of new chemical entities discovered by the pharmaceutical industry are poorly soluble or lipophilic compounds, which lead to poor oral bioavailability, high intra and inter subject variability and lack of dose proportionality.[1] Efforts are ongoing to enhance the oral bioavailability of lipophilic drugs in order to increase their clinical efficacy.[2] Self emulsifying drug delivery systems have been shown to be successful in improving the oral bioavailability of poorly water soluble and lipophilic drugs.[3]

Self emulsifying drug delivery systems (SEDDS) also called as self emulsifying oil formulation which are mixtures of oils and surfactants, ideally isotropic, and sometimes containing co-solvants, which emulsify spontaneously to produce fine oil in water emulsion when introduced into aqueous phase under gentle agitation.[4],[5] Self-nanoemulsifying (SNEDDS), self-microemulsifying (SMEDDS) and self-emulsifying drug delivery systems (SEDDS) to improve the oral bioavailability of poorly water-soluble drugs.[6-8]

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Losartan is an angiotensin II receptor blocker (ARB). It works by blocking a substance in the body that causes the blood vessels to tighten. Losartan relaxes the blood vessels and lowers the blood pressure. A lower blood pressure will increase the supply of blood and oxygen to the heart. [6]

It is BCS class III drug and it reaches mean peak plasma concentration approximately 1.5–2 hours post administration. In such cases it is very essential to enhance onset of action of a drug.[7]

Material and Methods

(Physicochemical and biopharmaceutical properties) involves the application of biopharmaceutical principles to the physicochemical parameters of drug substance and are characterized with the goal of designing optimum drug delivery system. Hence, the goals of preformulation studies are to choose the correct form of a substance, evaluate its physical properties and develop a safe, stable as well as therapeutically effective dosage form. Additionally, physical characters of drug and its interaction with delivery systems are also characterized that make a successful drug delivery system.

Material

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

Identification of Losartan Organoleptic Properties of Losartan

It is off White to off white free flowing crystalline powder. Its Molecular weight is 422.91 g/mol. It's Storage at room temperature between 15-30ºC. (IP 2007)

Melting point determination:

The temperature at which the solid and liquid forms of a pure substance can exist in equilibrium. As heat is applied to a solid, its temperature will increase until the melting point is reached. More heat then will convert the solid into a liquid with no temperature change. When the entire solid has melted, additional heat will raise the temperature of the liquid. The melting temperature of crystalline solids is a characteristic figure and is used to identify pure compounds and elements. Melting point was determined by Melting point Apparatus (Superfit India). The melting point of Losartan compared with the melting point given in monographs which ascertain the purity of molecules.

Table 1: Melting point of losartan

Drug	Standard(°C)	Observed (°C)
Losartan	184	181± 2

Solubility Profile: Solubility is a chemical property referring to the ability for a given substance, the solute, to dissolve in a solvent. It is measured in terms of the maximum amount of solute dissolved in a solvent at equilibrium. The solubility of a substance is the amount of that substance that will dissolve in a given amount of solvent. Solubility is a quantitative term. The terms soluble and insoluble are relative. A substance is said to be soluble if more than 0.1 g of that substance dissolves in 100 ml solvent. If less than 0.1 g dissolves in 100 ml solvent, the substance is said to be insoluble or, more exactly, sparingly soluble. The terms miscible and immiscible may be encountered when considering the solubility of one liquid in another. Miscible means soluble without limits.

Table 2: Solubility Profile of Losartan

S. No	Solvent	Solubility
1	Distilled Water	+
2	Methanol	+++
3	Ethanol	+++
4	n- hexane	_
5	Acetic acid	+++
6	Acetone	+++
7	Benzene	+++
8	0.1N HCL	+++

Where:

Insoluble (-): 1 part of solute requires 10,000 or more parts of solvent.

Slightly soluble (+): 1 part of solute requires 100 to 1000 parts of solvent.

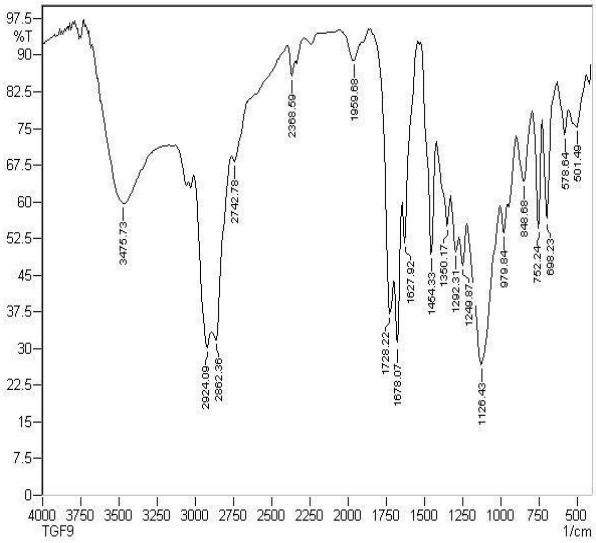
Sparingly soluble (++): 1 part of solute requires 30 to 100 parts of solvent.

Soluble (+++): 1 part of solute requires 10 to 30 parts of solvent.

Freely soluble (++++): 1 part of solute requires 1 to 10 parts of solvent.

Fourier Transfom Infra Red Spectroscopy (FT-IR)

FT-IR is a technique which is used to obtain an infrared spectrum of absorption, emission,



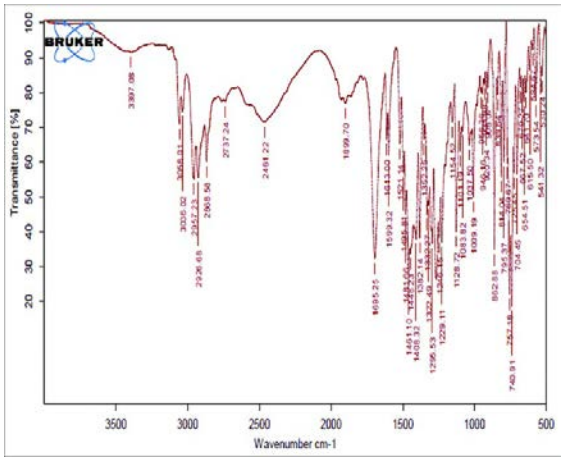


Figure 1: FTIR of (a) pure drug (b) gift sample losartan

Photoconductivity or Raman scattering of a solid, liquid or gas. IR spectrum of Losartan was taken out using KBr pellets (Bruker). Various peaks in IR spectra were intercepted for different group and were matched with reference IR spectra (IP 2007).

Partition Coefficient

The partition coefficient is defined as the ratio of un-ionized drug distributed between the organic and aqueous phase at equilibrium. The partition coefficient, P, of a drug is given by

Po/w = [Corg /Caq.]

Corg = concentration of drug in organic phase.
Caq. = concentration of drug in aqueous phase

The partition coefficient of Losartan was determined in n -octanol: water. 10mg of drug was accurately weighed and transferred into a separating funnel containing 10ml each of n-octanol.

The mixture was shaken using wrist action shaker for 4 hrs until equilibrium was reached. Phases were separated using the separating funnel and the aqueous phase and oil phase was analyzed for the amount of drug after appropriate dilution using EI double beam spectrophotometer 1372 UV-Spectrophotometer.

Table 3: Partition co-efficient of Losartan

S.no	Solvent system(s)	Partition co-efficient
1	n-octanol/water	Log p=0.14

Determination of absorption maxima (λmax) Organic molecules in solution when exposed to light in the ultraviolet region of the spectrum absorb light of particular wavelength depending on the types of electronic transition associated with the absorption. The Ultraviolet/visible spectroscopy has been used for structural validation of the drug. Absorption maxima of losartan were determined by preparing 10µg/ml solution of Losartan in methanol. This solution was scanned in UV spectrophotometer (EI double beam UV-VIS spectrophotometer UV/visible model 1372), in the range of 200-400nm. The λmax of the drug was determined from the spectra obtained. For losartan absorption

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maxima were observed at value of 251nm. The value of 251nm was chosen for the development of the present procedure.

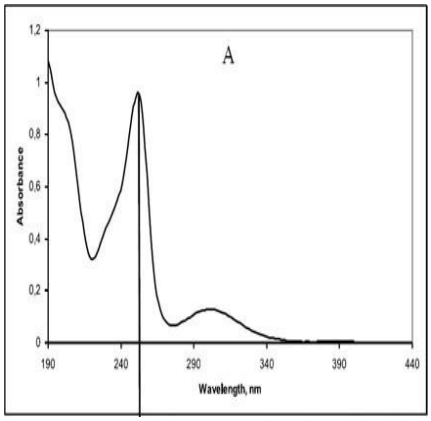

Figure 2: Absorption maxima of losartan

Preparation of standard curve of losartan

Before the selection of working concentration range we have tried various concentration ranges to find out conc. range obeying beer's Lambert law i.e. 2-20. Stock solution of losartan was prepared by dissolving 100mg (accurately weighed) of standard in 100ml losartan of methanol. Stock solution was suitably d losartan iluted to give a concentration of 10µg/ml. Working standard solution 100µg/ml was made from the stock solution by suitably diluted with methanol aliquots were prepared by pipetting 0.2, 0.4, 0.6, 0.8, 1.0, 1.2, 1.4, 1.6, 1.8, and 2.0 µg/ml from the working standard solution and suitably diluted with methanol in 10ml volumetric flask to give concentration of 2, 4, 6, 8, 10, 12, 14, 16, 18 and 20µg/ml. For losartan absorbance were recorded at 251 nm respectively against a reagent blank and Standard curve was plotted as shown in figure 5 and table 5.

Table 4: Data of Standard curve of Losartan using UV spectrophotometer

S.no	Concentration µg/ml	Absorbance	Statistical Parameters
1	2	0.231	
2	4	0.445	
3	6	0.615	**Equation of line**
4	8	0.813	*Y=0.963x+0.039*
5	10	1.012	**Correlation coefficient**

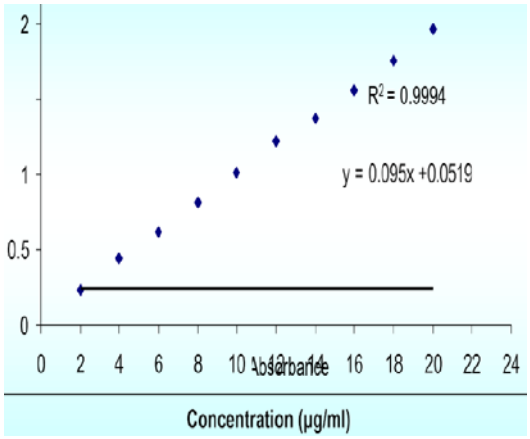

Figure 3: Standard curve of Losartan

Result and Discussion

The drug Losartan was gifted by M/S Medley lab, Jammu and identified as per tests prescribed in Pharmacopoeia of India (2007). The preliminary study was performed for the identification of drug based on melting point, solubility, IR-Spectroscopy, Partition coefficient and by λ max determination. The Melting point of Losartan was found to be 181±2°C whereas; the melting point of standard Losartan is 184°C.

The solubility profile of Losartan revealed that it is Soluble in Methanol, Ethanol, Acetic acid, Acetone, Benzene and 0.1N HCL, slightly soluble in distilled water and insoluble in n- hexane. An infrared spectrum of provided drug was found to be in concordant with the reference infrared spectrum of the Losartan. The IR-Spectrum of Losartan was in concordance with the standard. The partition coefficient of Losartan in n-octanol/water solvent system was found to be log P= 0.13 that was similar to that of standard of Losartan. Partition coefficient value of Losartan also revealed & it is hydrophilic in nature. Solution of Losartan in methanol was scanned in the U.V. range of 200-400 nm using EI double beam UV-VIS spectrophotometer UV/Visible model 1372 as prescribed in I.P. 2007. The Spectrophotometric method of analysis of Losartan at λ max 251.0 nm was found to be reproducible and highly sensitive. The standard curve of Losartan was prepared in methanol

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solution (pH 7.4) at λ max 251.0 nm. The data were regressed to obtain the straight line. The correlation coefficient 1.002 was observed in all the cases, which indicated that, the drug follows Beer-Lambert's law in the concentration range of 2-20 µg/ml. The Result of all preliminary study showed that the drug Losartan is pure and met all the standards as per IP 2007.

Preparation and Characterization

The aim of present work was to prepare and characterize SEDDS of Losartan to enhance solubility and bioavailability of hypolipidemic drug. Self-Emulsifying Drug Delivery System was prepared by simple emulsification technique as reported by Maulik.

Determination of saturation solubility of Losartan in different vehicles: The most important criterion for the screening of components for emulsion is the solubility of poorly soluble drug in oils, surfactants and co surfactants. The solubility of Losartan in various oils was determined by adding an excess amount of drug in 2 ml of selected oils (castor oil, soya bean oil, sunflower oil, oleic acid) and surfactants (tween-20, tween-80, span-20, span-80, PEG-200, PEG-400, and Glycerin) in 5 ml capacity stopper vials, and mixed by vortexing. The mixture vials were then kept at 25±1.0ºC in an ultra sonicator for 12 h. The sample was centrifuged at 1000 rpm for 10 min. The supernatant was taken and an aliquot of the supernatant was diluted with methanol and the concentration of Losartan was determined in oils using UV Spectrophotometer (EI double beam UV-VIS spectrophotometer UV/Visible model 1372) at 251 nm.

Table 5: Solubility of Losartan in various vehicles

S.no	Name of vehicles	Solubility found (mg/ml)
1	Castor oil	67.1
2	Soybean oil	57.6
3	Oleic acid	80.5
4	Sunflower oil	40.2
5	Tween-20	56.4
6	Tween-80	82.9
7	Span-20	65.5
8	Span-80	70.9
9	Glycerin	68.7
10	PEG-200	60.9
11	PEG-400	78.2

Formulation design:

Formula for the preparation of Self-emulsifying drug delivery system of Losartan is given in Table. The various formulation i.e. F1 to F6 were prepared.

Preparation of SEDDS:

This involved mixing of different oils, surfactant, co-surfactant and co-solvent. First weighed amount of Losartan was dissolved in ethanol by continuous stirring in a beaker until it totally dissolved. Then amount of oleic acid was added slowly with continuous stirring into drug-ethanol mixture. In another beaker appropriate amount of PEG-400 was added to Tween-80 and mixed properly by continuous stirring with a glass rod. After continuous stirring the mixture of Tween-80 and PEG-400 were added to the drug- ethanol mixture by magnetic stirring at 100 rpm for 30 minute. The formulation of SEDDS was stored in well closed container for its further characterization. (Maulik et al; 2010)

Table 6: Formulation of SEDDS

Formulation	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. In the above formulation design the F5 formulation is selected for the further study.

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Table 7: Assessment of self emulsification for various SEDDS formulations

Formulation	Grade
F1	C
F2	A
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 minutes
Grade D: Dull, grayish white emulsion having slightly oily appearance that is slow to emulsify longer than 2 minutes.
Grade E: Formulation, exhibiting either poor or minimal emulsification with large oil globules present on the surface.

Characterization of formulation:

The obtained SEDDS formulation (F5) was selected and characterized for various attributes viz. Assessment of emulsification time, Emulsification time, Droplet size analysis, Zeta potential measurement , transmission and Electron Microscopy, Viscosity Determination, drug content, percentage transmittance, Italic drug release study and stability study.

Optical microscopy:

The opted formulation (F5) of SEDDS observed under optical microscope (Lambed) and it was found that the developed formulation contained the droplets in emulsion

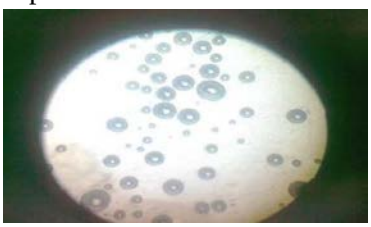

Figure 4: Photograph of formulation (F5) of SEDDS of Losartan under optical microscope.

Assessment of self emulsification:

The efficiency of emulsification was assessed0 using a standard US pharmacopoeia XXIII dissolution apparatus type II. One gm of formulation was added drop wise to 200ml of at 37 ˚C. Gentle agitation was provided by a standard stainless steel dissolution paddle at 60rpm. The Italic performance of the formulation was visually assessed using the following grading system.**(khoo et al,1998)**

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 minutes
Grade D: Dull, grayish white emulsion having slightly oily appearance that is slow to emulsify longer than 2 minutes.
Grade E: Formulation, exhibiting either poor or minimal emulsification with large oil globules present on the surface.

Table 8: Assessment of emulsification time (F5)

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

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) (**Patil et al; 2004**)

Table 9: Droplet size analysis of SEDDS formulation (F5)

Formulation code	Parameter	Result
F5	Droplet size	125.89 nm

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

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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. **(Singh et al 2009)**

Table 10: Zeta potential of SEDDS formulation (F5)

Formulation code	Parameter	Result
F5	Zeta potential	-25.7 mV

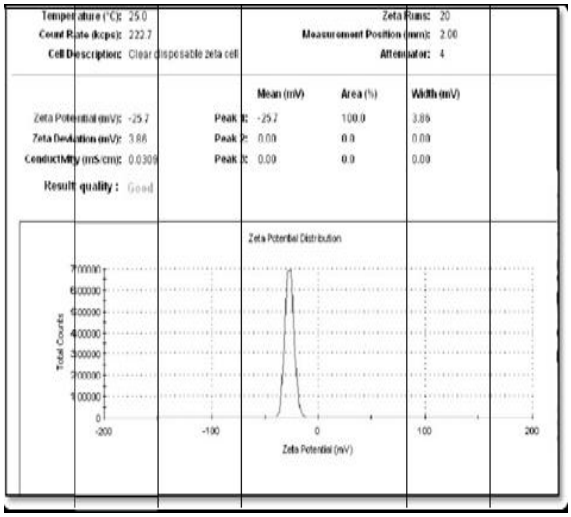

Figure 5: Zeta potential of SEDDS formulation (F5).

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 created problem in pourability. SEDDS of losartan (1ml) was diluted with the distilled water in a beaker with constant stirring on magnetic stirrer. Viscosity of the resultant emulsion and initial SEDDS was measured using Broolfield viscometer (DV-III Ultra Brookfield). The data of viscosity of SEDDS formulation (F5) was recorded in the (table 12) **(Yogeshwar, Vandana 2009)**

Table 11: Viscosity of SEDDS formulation (F5)

Formulation code	Parameter	Result
F5	Viscosity	12.2±0.2 cP

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 251 nm using UV-Visible 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 **(Snehal, Dhomne 2012)**

Table 12: Drug Content of SEDDS Formulation (F5)

Formulation code	Parameter	Result
F5	Drug content	97.65±1.37

Percentage transmittance

Percent transmittance proved the transparency of formulation. The percent transmittance of the system is measured at particular wavelength using UV spectrophotometer (EI double beam UV-VIS spectrophotometer UV/Visible model 1372) by using distilled water as blank (**Sapra et al., 2012).**

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A total of 1mL SEDDS formulation was diluted 100 times with distilled water. Percentage of transmittance was measured spectrophotometrically (EI double beam spectrophotometer 1372 UV Spectrophotometer) at 251 nm using water as a blank.

Table13: Percentage transmittance of SEDDS formulation

Formulation code	Parameter	Result
F5	Percentage transmittance	97.45±1.78

***In vitro* dissolution**

The quantitative in-vitro drug release from formulation was studied to assess if self emulsifying properties remain consistent. The USP XXII, dissolution apparatus (Electrolab TDT-06l) used to study the release of the drug from the oil in the aqueous system. Hard gelatin capsule containing SEDDS was tied to paddle to prevent the capsule from floating 900 ml dissolution media were used standard phosphate buffer solution pH 7.4.

To compare different SEDDS, dissolution studies were done at 37±0.5ºC, using paddle rotating at 75 rpm, 1ml sample was withdrawn at 30, 60, 90, 120, 150, 180 minutes. The sample volume of fresh media replaces the withdrawn sample. Sample was filter through whatmann filter paper and analyzed spectrophotometrically (EI double beam UV-VIS spectrophotometer UV/Visible model 1372) at 251 nm. The drug release from the SEDDS formulation was found to be significantly higher as compared with that of pure drug and marketed preparation (Cozaar 10 mg).

Table 14: Percentage drug release of F5, pure drug and marketed formulation

S.no	Time(min.)	Formulation F5	Pure drug (losartan)	Marketed formulation Cozar
1	0	0	0	0
2	30	22.31	7.12	14.29
3	60	32.18	10.34	21.13
4	90	44.23	15.46	31.89
5	120	55.13	22.49	43.01
6	150	67.09	26.96	53.11
7	180	82.36	32.11	61.09

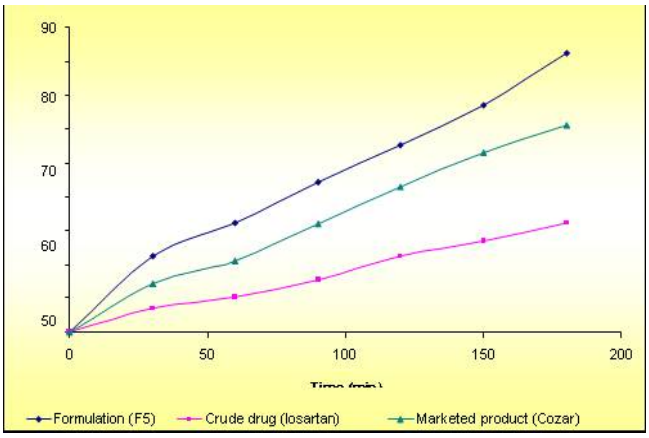

Figure 6: *In vitro* drug release profile of F 5, pure drug and marketed formulation

Solubility of Losartan in the oils, surfactant and co-surfactant was shown in the Table. All the components are pharmaceutically acceptable for oral administration and fall under GRAS (Generally recognized as safe) category. The solubility of the Losartan was tested in different oils phase that is Oleic acid, Soyabean oil, Castor oil andsunflower oil and maximum solubility was determined in Oleic acid 80.5 mg/ml and was selected as oily phase for SEDDS formulation. The solubility of the drug was tested in different surfactant tween-20, tween-80, span-20, span-80 and co-surfactant PEG-200, PEG-400, glycerin and maximum solubility determined 82.9 mg/ml of tween-80 as a surfactant phase and 78.2 mg/ml of PEG-400 as a co-surfactant phase. It was selected as surfactant for SEDDS formulation. Losartan is soluble in Ethanol and therefore Ethanol was used in formulation as co-solvent.

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 the further study that is used for characterization under various parameters. The opted formulation (F5) of SEDDS observed under optical microscope (Labmed) and it was found that the developed formulation contained the droplets in emulsion.

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.

The emulsification time of SEDDS was 19±5.51 seconds which resulted in good tendency for emulsification. 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. The zeta potential value of SEDDS (F5) was found to be -25.7 mV negative charge indicates that the emulsion particles were stable.

The TEM photograph shows the surface morphology of the SEDDS (F5) as seen in figure 8 the nanosized droplets as discreet 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. 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.

The percentage drug content was found to be 97.65±1.37 which is maximum and thus resulted in maximum drug release. The result of percentage transmittance was shown 97.45±1.78. This result indicated the high clarity of SEDDS. The greater the particle size, oil globules may reduce the transparency of micro emulsion and thereby values of percentage transmittance.

The formulation of SEDDS (F5) showed greater extent of drug release that is in 90 mins 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.

SEDDSs are isotropic mixtures of oils and surfactants; sometimes it contains co-solvents and it can be used for the design of formulations in order to improve the oral absorption of highly lipophilic compounds. Losartan is a hydrophobic and highly permeable drug which belongs to class II of biopharmaceutical classification system (BCS).

Low aqueous solubility of Losartan leads to high variability in absorption after oral administration. The present study was carried out for the formulation development of Losartan loaded self emulsifying drug delivery system (SEDDS) with the aim of enhancement its solubility as well as oral bioavailability. According to the preformulation study of drug it was found to be white to off-white, crystalline powder that was similar in physical appearance as mentioned in I.P. 2007. The Melting point of Losartan was found to be 181 ± 2°C whereas; the melting point of standard Losartan is 184°C. The solubility profile of Losartan at room temperature revealed that it was Soluble in Methanol, Ethanol, Acetic acid, Acetone, Benzene and 0.1N HCL, slightly soluble in distilled water but insoluble in n-hexane. An infrared spectrum of provided drug was found to be concordant with the reference infrared spectrum of the Losartan. The partition coefficient of Losartan in n-octanol/water solvent system was found to be log P= 0.13 that was similar to that of standard of Losartan. Partition coefficient value of Losartan also revealed & it is hydrophilic in nature. Solution of Losartan and methanol was scanned in the U.V. range of 200-400 nm using EI double beam UV-VIS spectrophotometer UV/Visible model 1372 as prescribed in I.P. 2007. The Spectrophotometric method of analysis of Losartan at λmax 251 nm was found to be reproducible and highly sensitive. The standard curve of Losartan was prepared in methanol solution (pH 7.4) at λmax 251 nm. The data were regressed to obtain the straight line. The correlation coefficient 0.999 was observed in all the cases, which indicated that, the drug follows Beer-Lambert's law in the concentration range of 2-20 µg/ml. The Result of all preliminary study showed that the drug Losartan was pure and met all the standards as per IP 2007.

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 concentration of oil, surfactant and cosurfactant by simple emulsification technique and preparation F5 is selected for its further evaluation according to its good solubility parameters and assessment of self emulsification. (Table 8) 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, Viscosity Determination, Drug content, In vitro dissolution study and stability study. The opted formulation (F5) of SEDDS observed under optical microscope (Labmed) and it was found that the developed formulation contained the droplets in emulsion. 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. The emulsification time of SEDDS was 19±5.51 seconds which resulted in good tendency for emulsification. (Table 9) 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. The zeta potential value of SEDDS (F5) was -25.7 mV negative charge indicates that the emulsion particles were stable.

The TEM photograph showed spherical surface morphology of SEDDS (F5) which resulted in higher drug loading. 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 befaster. (Table 12) The percentage drug content was found to be 97.65±1.37 which is maximum and thus resulted in maximum drug release. This result indicated the high clarity of SEDDS. The greater the particle size, oil globules may reduce the transparency of micro emulsion and thereby values of percentage transmittance.

The formulation of SEDDS (F5) showed greater extent of drug release that is in 90 mins 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.

Conclusion

The present research was mainly aimed at improving the solubility and bioavailability of otherwise poorly soluble BCS class II drug Losartan. The present study deals with formulation of a Losartan based Self emulsifying drug delivery system of poorly water soluble drug. SEDDS are the isotropic mixtures of oil, surfactant, co surfactant and drug that form oil in water emulsion when introduced into aqueous phase under gentle agitation. The present research work describes a Self Emulsifying Drug Delivery System (SEDDS) of Losartan using oil components (Oleic acid), surfactants (Tween 80), Co- surfactant (PEG-400) and Solvent (Ethanol). Losartan is an HMG-CoA inhibitor with limited water solubility, which accounts for a low and variable oral bioavailability (20%). Hence, the main objective of study was to formulate SEDDS of Losartan in order to achieve a better dissolution rate which would further help in enhancing oral bioavailability.

From the studies performed it was concluded that, prepared liquid SEDDS has good self emulsification efficiency and having globule size in nanometer range which may be physiologically stable. The mixtures consisting of oil (oleic acid) with surfactant (tween 80), co-surfactant (PEG 400) were found to be optimum formulations. Prepared SEDDS formulations were tested for emulsifying properties and the resultant emulsion was evaluated for assessment of efficiency of self emulsification, emulsification time, viscosity, zeta potential, percentage transmittance, transmission electron microscopy, drug content and Italic dissolution.

The formulation was found to show a significant improvement in terms of the drug release with above 83% release of drug within 180 mins. Thus, Self emulsifying formulation of Losartan was successfully developed. Oral bioavailability of poorly water-soluble compounds is increased by using this formulation system. So in future the SEDDS may be used as a vital tool in reducing the dose size in the formulation. The present study demonstrated successful preparation of self emulsifying drug delivery systems of Losartan with enhancing its bioavailability

Thus our studies confirmed that SEDDS can be used as a possible alternative to conventional oral formulation of BCS class II drugs (poorly water soluble drugs). Results further conclude that

SEDDS can be explored as a potential drug carrier.

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