Formulation and Characterization of Losartan-Loaded Self-Emulsifying Drug Delivery System

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Abstract

The present study focuses on the formulation and characterization of a Losartan-loaded Self-Emulsifying Drug Delivery System (SEDDS) to overcome the problem of poor water solubility and limited oral bioavailability. Losartan, an angiotensin II receptor blocker, exhibits low aqueous solubility and hence poor absorption through the gastrointestinal tract. In this study, various oils, surfactants, and co-surfactants were screened for solubility, and formulations were optimized based on self-emulsification efficiency, droplet size, zeta potential, and drug release characteristics. The optimized formulation (F5) demonstrated a rapid emulsification time, stable nano-sized droplets, and significant enhancement in drug release compared with pure Losartan and marketed formulations. The results indicated that SEDDS could serve as a promising strategy for improving the solubility and bioavailability of poorly water-soluble drugs like Losartan.

Keywords: Losartan; Self-Emulsifying Drug Delivery System (SEDDS); Solubility; Bioavailability; Lipid-based formulation.

1. Introduction

Drugs play an important role in our health management. Due to their importance the drugs have been classified as “essential commodity.” The forms in which drug substances are presented in the market are called the dosage forms i.e. tablets, capsules, ointments, syrups etc.

The desirable properties of dosage form are following:

1. It should be convenient to handle, store and use for better patient compliance.

2. It should be stable during storage (shelf-life) and use. During storage the physical, chemical and therapeutic integrity of the dosage form should be maintained.

3. It should protect the drug substances and conceal the disagreeable taste or odour. During recent years the discovery of a drug and introduction into the market has become most costly affair usually running into several crores of rupees. Thus very few new drugs are appearing in the market. In conventional drug delivery system only a fraction of dosereaches to systemic blood circulation and hence most of the dose is wasted and affected by the gastric environment, pH conditions, and reaction with the gut walls, GI motility and presence of food in the GI tract. Due to this the drug release pattern from dosage form is affected which in turn affect the therapeutic pattern. This results in longer period of dosing, patient inconvenience and other systemic effects **(Jain and Sharma 2008)** The method by which a drug is delivered can have a major effect on its efficacy. Some drugs have an optimum concentration range within which maximum benefit is derived and concentrations above or below this range can be toxic or produce no therapeutic benefit at all. On the other hand, very slow development in the efficacy of the treatment severe diseases hase suggested agrowing need for a multidisciplinary approach to the delivery of therapeutics to targets in tissues. From this, new ideas on controlling the pharmacokinetics, pharmacodynamics, non- specific toxicity, immunogenicity, biorecognition, and effectiveness of drugs were generated. These new strategies, often called drug delivery systems (DDS) **(Costas et al 2005)** The oral route is most popular route among all the route of administration. Approximately 40% of new drug candidates have poor water solubility and oral delivery of such drug is frequently associated with low bioavailability, high intra- and inter –subject variability and a lack of dose proportionality.(Sharma et al; 2011) in recent years, the formulation of poorly soluble compounds present interesting challenges for formulation in the pharmaceutical industry. Approximately 40% of new chemical drugs moieties has poor aqueous solubility and it is a major challenges to modern drug delivery system. The rate limitation step for the absorption of these types of drug is their solubilisation in the gastrointestinal tract. The drug with poor aqueous solubility and high permeability are classified as class II drug by biopharmaceutical classification system.

2. Materials and Methods

2.1 Materials:

Losartan was obtained as a gift sample from Medley Laboratories, Jammu, India. Oleic acid, soybean oil, castor oil, PEG-200, PEG-400, Tween 20, Tween 80, Span 20, Span 80, and ethanol were used as formulation excipients.

2.2 Preformulation Studies of losartan

2.2.1 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)

2.2.2 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.

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

Table 1: Melting point of losartan

2.2.3 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 whenconsidering the solubility of one liquid in another. Miscible means soluble without limits.

S. No	**Solvent**	**Solubility**
1	Distilled water	+
2	Methanol	+++
3	Ethanol	+++
4	n- hexane	-
5	Acetic Acid	+++
6	Acetone	+++
7	Benzene	+++
8	0.1 N HCL	+++
9	Acetonitrile	+++
10	N, N-Dimethyl formamide	+++

Table 2: Solubility Profile of losartan

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.

3 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 Maulik et al; 2010.

3.1 Preparation of SEDDS:

This involved mixing of different oils, surfactant, co-surfactant and co-solvent shown in. 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)

Formulation	**Drug Losartan in (mg)**	**Tween 80 in (ml)**	**PEG 400 in (ml)**	**Ethanol in(ml)**	**Oleic acid in (ml)**	**Glycer in 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

Table 3: Formulation of SEDDS

3.2 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 8) In the above formulation design the F5 formulation is selected for the further study and characterized for various parameters.

Formulation	
F1	C
F2	A
F3	D

F4	C
F5	A
F6	B

Table 4: Assessment of self emulsification for various SEDDS formulations

***Grade A* :** Rapidly forming emulsion having a clear or bluish appearance. 61
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.

3.3 Formulation of SEDDS:

Formulations were prepared by dissolving the drug in the selected oil phase, followed by addition of surfactant and co-surfactant under continuous stirring until a clear isotropic mixture was obtained. The formulations were evaluated for self-emulsification efficiency, emulsification time, droplet size, and zeta potential.

3.4 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.

3.4.1 Optical microscopy:

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

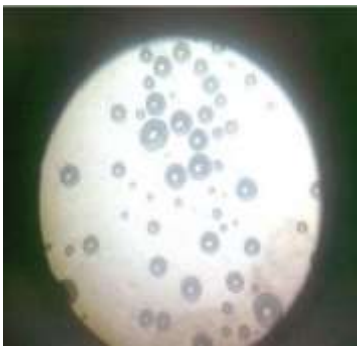


Figure 1: Photograph of formulation (F5) of SEDDS of Losartan under optical microscope.

3.4.2 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.

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

Table 5: Assessment of emulsification time (F5)

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

Formulation code	Parameter	Result
F5	Droplet Size	125.89 nm

Table 6: Droplet size analysis of SEDDS formulation (F5)

3.4.4 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 7) (Figure 2) (Singh et al 2009)

Formulation code	Parameter	Result
F5	Zeta potential	-25.7 mV

Table7: Zeta potential of SEDDS formulation (F5)

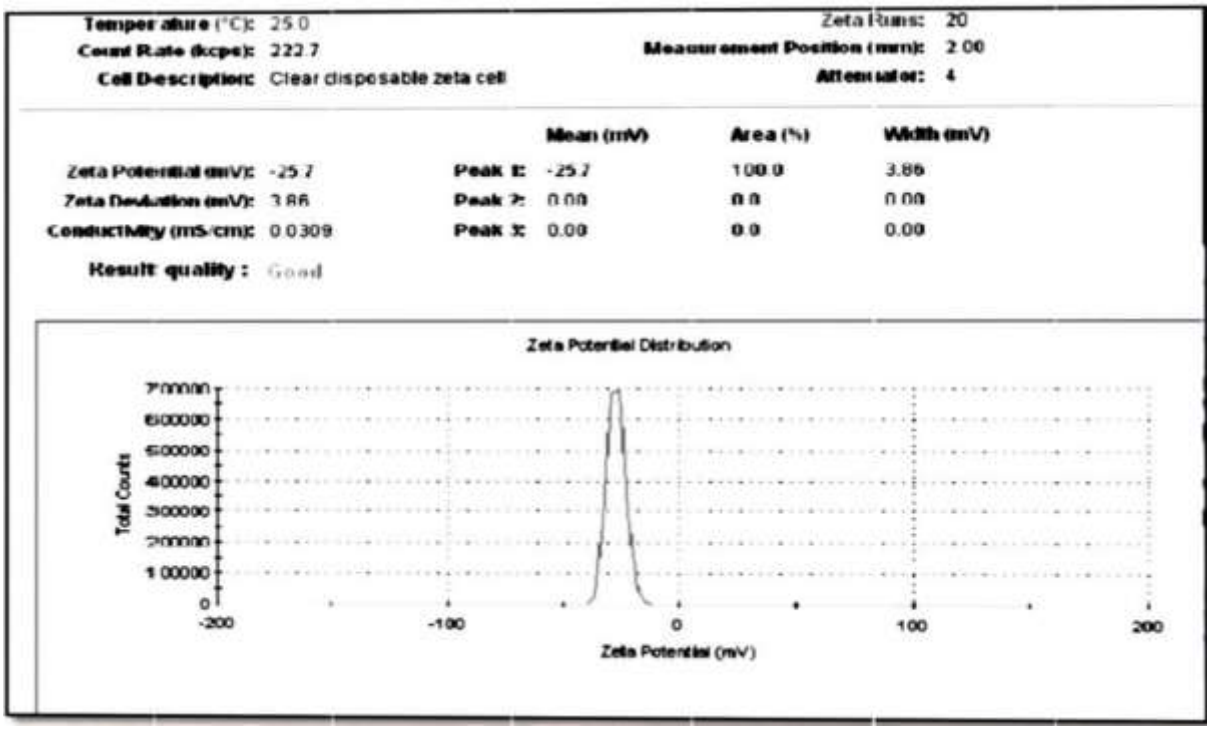


Figure 2: Zeta potential of SEDDS formulation (F5).

3.4.5 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 Brooklfield viscometer (DV-III Ultra Brookfield). The data of viscosity of SEDDS formulation (F5) was recorded in the (table 12) **(Yogeshwar, Vandana 2009)**

Formulation code	Parameter	Result
F5	Viscosity	-25.7 mV

Table 8: Viscosity of SEDDS formulation (F5)

3.4.6 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 (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 13) **(Snehal, Dhomne 2012)**

Formulation code	Parameter	Result
F5	Drug content	97.65±1.37

Table 9: Drug Content of SEDDS Formulation (F5)

3.4.7 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).** 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. (Table 14)

Formulation code	Parameter	Result
F5	Percentage transmittance	97.45±1.78

Table10: Percentage transmittance of SEDDS formulation

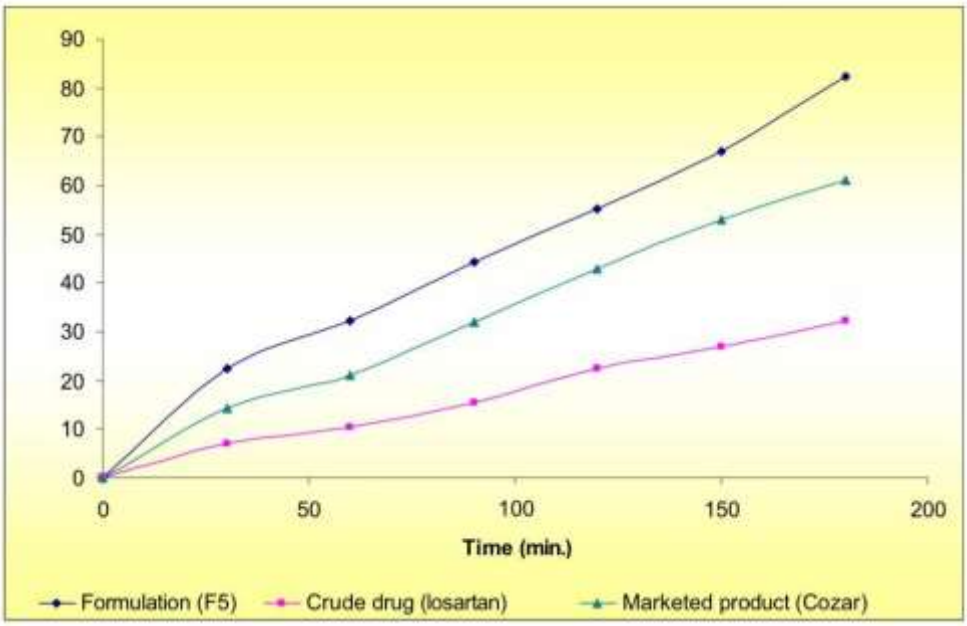
3.4.8 In vitro dissolution

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 theSEDDS formulation was found to be significantly higher as compared with that of pure drug and marketed preparation (Cozaar 10 mg). (Table 11)(Figure 3)

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

Table11: Percentage drug release of F5, pure drug and marketed formulation



Formulation (F5) Crude drug (losartan) Marketed product (Cozar)

Figure 3– *In vitro* drug release profile of F 5, pure drug and marketed formulation

4. Conclusion

The study successfully formulated and characterized a Losartan-loaded Self-Emulsifying Drug Delivery System (SEDDS) with improved solubility and dissolution profile. The optimized formulation (F5) demonstrated excellent self-emulsification, nano-sized droplets, and enhanced drug release compared to the pure drug and marketed formulations. These findings suggest that SEDDS can serve as an effective strategy for enhancing the oral bioavailability of poorly water-soluble drugs such as Losartan, leading to improved therapeutic efficacy and patient compliance.

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