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## FORMULATION AND EVALUATION OF LOSARTAN SELF MICROEMULSIFYING DRUG DELIVERY SYSTEM

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### ABSTRACT

This study presents the formulation and evaluation of a self-microemulsifying drug delivery system (SMEDDS) for Losartan, an angiotensin II receptor blocker widely used in the treatment of hypertension. Losartan is characterized by poor aqueous solubility, which limits its bioavailability and therapeutic effectiveness. The aim of this study was to enhance the solubility and bioavailability of Losartan by developing a SMEDDS formulation. Based on their solubilizing ability for Losartan, oils, surfactants, and co-surfactants were selected to formulate the SMEDDS. The optimal composition and ratio of components were determined through various preformulation studies. Based on the optimized SMEDDS, a stable microemulsion is demonstrated. The SMEDDS also maintained excellent stability over a wide range of storage conditions, and did not show any significant differences in their physical properties or drug content. According to the results, the developed Losartan SMEDDS formulation effectively enhances the solubility and dissolution rate of Losartan, which may result in better oral bioavailability and therapeutic outcomes when compared with existing formulations. As a result of this novel delivery system, Losartan's solubility issues may be overcome, which could lead to improved patient compliance and better management of the drug.

**Key words:** Losartan, Hypertension, Gastric, Micro Emulsion

### INTRODUCTION

The advancement in the field of pharmaceutical technology has focused on the need to develop delivery system for targeted delivery of peptides and protein drugs. Among these self-microemulsifying drug delivery system (SMEDDS) is a superior choice for delivery of macromolecular drugs in multiple scenarios. It not only offers improved oral bioavailability of drugs by allowing efficient drug transport across absorptive membranes but also shields encapsulated drugs against severe enzymatic hydrolysis in GIT (Mudassir, J. *et al.* 2023). Moreover, simple manufacturing processes without consumption of any external heating or energy aid also favors delivery of heat labile proteins and peptides through the system.

However, hydrophilic nature of proteins makes it almost impossible to dissolve in lipophilic oil phase of system. To deal with the issue, hydrophobic ion pair technique (HIP) was introduced by researchers that enhance the lipophilic nature of proteins and peptides simply by incorporating a hydrophobic chain in the structure (Deepak Kaushik *et al.* 2017). The technique involves complexation of proteins' ionizable groups with counterions of complex forming agents such as amphiphilic molecules or surfactants at a particular pH. Complex is usually formed between basic amino acids of proteins primarily lysines and arginines and anionic surfactants. In the presence of excess of oppositely charged ions with higher affinity, complex dissociates into its components. Similar phenomena were used to encapsulate insulin in SMEDDS.

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## Self Microemulsifying Drug Delivery Systems (SMEDDS)

Self MicroEmulsifying Drug Delivery Systems (SMEDDS) are defined as isotropic mixtures of natural or synthetic oils, solid or liquid surfactants, or alternatively, one or more hydrophilic solvents and co-solvents/surfactants. Upon mild agitation followed by dilution in aqueous media, such as GI fluids, these systems can form fine oil in water (o/w) emulsions or microemulsions (SMEDDS). Self microemulsifying formulations spread readily in the gastro intestinal tract and the digestive motility of the stomach and the intestine provide the agitation necessary for self-emulsification. SEDDS typically produce emulsions with a droplet size between 100 and 300 nm while SMEDDS form transparent microemulsions with a droplet size of less than 50 nm. An additional advantage of SMEDDS over simple oily solutions is that they provide a large interfacial area for partitioning of the drug between oil and water. Thus, for lipophilic drug compounds that exhibit dissolution rate limited absorption, these systems may offer an improvement in the rate and extent of absorption and result in more reproducible blood time profiles and have been shown to enhance the oral bioavailability of lipophilic drugs such as cyclosporine, halofantrine, ontazolast and progesterone. The ease of dispersion and the very small particle size of the resultant colloidal microemulsion have been viewed as the principal reasons for their utility in the delivery of lipophilic drugs (Vaibhav S *et al.*, 2023) Consequently, most of the commercially available lipid formulations are complex mixtures of lipids, surfactants, and cosolvents/cosurfactant constructed to improve drug solubility in the formulation (and therefore increase drug pay load) and also to maximize dispersion of the dose form on exposure of the capsule fill to the GI contents. When compared with emulsions, which are sensitive and metastable dispersed forms, SMEDDS are physically stable formulations that are easy to manufacture. Microemulsions are readily distinguished from normal emulsions by their transparency, their low viscosity, and more fundamentally their thermodynamic stability (Mulla S *et al.*, 2024).

## METHODOLOGY

### Analytical method:

#### Preparation of 0.01 N HCl solution:

To prepare a stock solution of 101 µg/ml, losartan was weighed accurately and dissolved in 100 ml of 0.01 N HCl.

#### Calibration curve of Losartan:

##### Preparation of calibration curve of Losartan:

Losartan 10 mg was dissolved in a 10 ml 0.01N HCl solution to prepare a stock solution containing 100 µg/ml in a 100 ml volumetric flask. The stock solution

was diluted to 10 ml with 0.01N HCL to produce a 10 ml volumetric flask containing 10µg/ml solution. The stock solution was concentrated to produce concentration solutions of 5-30 µg/ml. A UV spectrophotometer at a wavelength of 227.4 nm was used for the analysis of the samples.

### List of Materials:

Losartan, Polysorbate 80, Capryol 90, Tween 80, Polyethylene glycol 400, Labrasol, Peceol, Transcutol P, Captex 200, Captex 200P, Isopropyl myristate, PlurolOlieque, Labrofil, Capmul MCM.

### List of Equipment's:

Digital weighing balance, Digital pH meter, Magnetic Stirrer, Malvern zetasizer, Dissolution apparatus, UV spectrophotometer.

### Preparation of Losartan SMEDDS:

Table 3 shows a series of SMEDDS formulations utilizing a variety of oils, surfactants, and co-surfactants. Losartan's dose did not differ in any of the formulations (i.e., 10 mg). SMEDDS should be calculated so that it completely dissolves the drug (single dose). Losartan was added to the mixture in the amount of 10 mg. After the mixture had been mixed, a vortex mixer method was used to mix the components, and the mixture was heated at 37 degrees Celsius after the components had been combined. The mixture was stored at room temperature in order to preserve its quality. A SMEDDS was prepared by combining oils, surfactants, cosurfactants, and drugs. Various surfactants and cosurfactants were used to prepare 60 formulations

## CHARACTERIZATION OF SMEDDS OF LOSARTAN

### Viscosity and pH:

Viscosity measurements were used to determine the rheological properties of formulations. A Brookfield LVDV 111+ CP viscometer at 30°C was used in conjunction with a CPE 42 spindle at 5 revolutions per minute. Formulations were pH-measured using a pH meter.

### Dispersibility test:

The effectiveness of oral SMEDDS self-emulsification was evaluated using the USP XXII dissolution apparatus 2. The mixtures were mixed at 37 degrees Celsius with 500 ml of water and 1 milliliter of each formulation. Gentle agitation was provided by the dissolution paddle rotating at 50 revolutions per minute. The formulations' in vitro performance was assessed visually based on the grading system. (Kommuru TR *et al.*, 2001)

### Drug content:

It was determined that Losartan SMEDDS formulation contained the desired amount of drug using a UV spectroscopic method. Methanol was used as a solvent to prepare the 10 µg/ml aliquot of SMEDDS formulation. According to UV spectroscopic measurements, the samples have a wavelength of 227 nm.

#### Particle size distribution

In distilled water and 0.1 mol/l liquid HCl, a gram of SMEDDS was dispersed at  $37 \pm 0.5^\circ\text{C}$ . The emulsions were gently agitated for 10 minutes using a magnetic stirrer. The PSD and 3-potential of the final micro emulsion were also determined using this method.

#### % Transmittance Measurement:

The percent transmittance of various formulations was measured with a UV spectrophotometer at 227 nm while 0.01N HCL served as the blank.

#### Polydispersibility Index:

SMEDDS particles were dispersed in 100 ml of distilled water and 0.1 mol/l HCl at  $37 \pm 0.5^\circ\text{C}$  to determine particle size distribution. Ten minutes were spent gently agitating the emulsions with a magnetic stirrer.

#### In-vitro diffusion study:

The diffusion of drugs was studied in vitro using the dialysis bag method. The dialysis bag was soaked in 0.1 N HCl overnight, then used the next day for the experiment. As a dissolution medium, 500 ml of 0.1% HCL was infused with 1 ml of losartan SMEDDS, which was then placed in 1 ml of losartan SMEDDS at  $37 \pm 0.5^\circ\text{C}$ . A speed of 50 revolutions per minute was maintained throughout the paddle revolution. In regular intervals of five minutes, samples (5mL) were taken and replaced with aliquots of 0.1 N HCL. As well as the conventional capsule formulation, SMEDDS was compared to the suspension of pure drug. (Humberstone AJ *et al.* 1997 & Pouton CW *et al.*, 1997)

#### Stability of Losartan SMEDDS:

The losartan SMEDDS samples were sealed in ampoules and stored at 25 and  $40 \pm 0.5^\circ\text{C}$  for three months. During 0, 1, 2 and 3 months, duplicate samples were taken to assess sample stability. Particle size was determined by a particle size analyzer after dilution with water and 0.1 mol/l hydrochloric acid to assess physical stability. UV spectroscopy at 227 nm was used to measure Losartan's chemical stability (Gursoy RN *et al.* 2004 & Stegemanna S *et al.*, 2007)

## RESULTS AND DISCUSSION

#### Viscosity and pH:

A microemulsion system can be monitored using rheological techniques. It is possible to use a variety of oils and surfactants. A viscosity of less than 0.8 centipoise was found in all formulations. Based on the formulation, has a viscosity of 0.8 cP, which is similar to water's viscosity of 1.0. SMEDDS forms an o/w microemulsion with water as the external phase, exhibiting a similar viscosity to water. In view of these results, formulation c1 is a clear, transparent, and low viscous liquid. (Murdandea SB *et al.* 2008)

A pH measurement was also taken as another important parameter. Excipients used in the formulation determine the pH of the final preparation. A change in pH may affect the formulation's zeta potential, which can adversely affect its stability. All formulations had similar pH values, ranging from 5.2 to 5.9. Therefore, pH was not a determining factor in the formulation's stability. The drug should thus remain in the oil phase and not diffuse in the external phase. As the system's external phase is water, the pH of the water is displayed throughout the entire system. Losartan pH is acidic to neutral, which makes the formulations stable. (Strickley RG *et al.* 2004)

#### Dispersibility test:

If a micro emulsion formulation is diluted infinitely, its phase separation can result in poorly soluble drugs precipitating as micro emulsions form at a specific concentration of oil, surfactant, and water. During oral administration of microemulsions, surfactant located at the globule interface gradually desorbs due to dilution by gastrointestinal fluids. For surfactants to be thermodynamically driven, their concentration in aqueous phase must equal their CMC. Microemulsions prepared with nonionic surfactants were not significantly different from those prepared with simulated gastric or intestinal fluid or distilled water, respectively. (Tang J *et al.*, 2007) Due to their microemulsion characteristics, Grades A and B formulations have been selected for further research after passing the dispersibility test. For further investigation, we discarded formulations that scored in Grades C, D, and E of the Dispersibility test. Using a self-emulsifying formulation that falls within Grade C may be appropriate for self-emulsifying drug delivery. There were three percentages of oil in the formulations we selected against each other. These percentages were chosen based on the intensity of the oil concentrations and the amount of surfactant that was needed to solubilize the oil. In vitro release, globule size and viscosity were determined using the optimal formulations. (Kawakami K *et al.* 2002 & Lawrence MJ *et al.* 2000)

#### Particle size distribution (PSD):

In self-emulsification, the size of the droplets determines the rate and extent of the drug's release and

absorption. The bioavailability of emulsion may also be enhanced by smaller droplets. Water and 0.1mol/l HCl were used to dilute losartan SMEDDS. As can be seen from Table 2, Losartan SMEDDS have an average particle size of 0.30 microns. The optimal batch was R4IIB, which had a mean particle size of 10nm in water. In spite of the dispersion medium used, the resultant emulsion had a small mean size and narrow particle size distribution due to SMEDDS. It is also important to take into account the charge of SEDDS.

#### % Transmittance:

with a %T value of 96% were observed in other systems, suggesting a lack of clarity. Perhaps this phenomenon can be explained by the formulation having a larger particle size. Microemulsions that contain oil globules

may have reduced transparency due to their larger particle size. As shown in table 3, %T results are as follows.

#### Polydispersibility Index (PDI):

Polydispersibility, which determines the size range of particles in a system, is measured as follows:

$$= \frac{\text{No. of particles having size greater than 100nm}}{\text{No. of particles having size less than 100nm}}$$

PDI measures polydispersibility with an index known as Polydispersibility Index (PDI). SMEDDS are ideal when they have a wide distribution of nanoparticles with a maximum of 24% of particles smaller than 100 nanometers. The following data is shown in table 4.

**Table 1: Viscosity and pH of SMEDDS formulation**

| Formulation code | Viscosity (cP) | pH  |
|------------------|----------------|-----|
| C1               | 0.9771         | 5.4 |
| C2               | 0.9847         | 5.9 |
| C3               | 0.9664         | 5.6 |
| C4               | 0.9745         | 5.4 |

**Table 2: Particle size of the various SMEDDS formulations**

| Formulation code | Avg. Particle size |      |
|------------------|--------------------|------|
|                  | Water              | HCL  |
| C1               | 25.4               | 25.1 |
| C2               | 10.2               | 77.6 |
| C3               | 203                | 186  |
| C4               | 134                | 113  |

**Table 3: % Transmittance**

| Period Days | % T      |          |
|-------------|----------|----------|
|             | 25°C     | 40°C     |
| 0           | 99.4±0.5 | 99.4±0.5 |
| 15          | 99.2±0.6 | 99.5±0.4 |
| 30          | 99.3±0.5 | 98.1±0.7 |
| 45          | 99.2±0.6 | 97.4±0.2 |
| 60          | 99.1±0.6 | 94.3±0.5 |
| 90          | 99.5±0.6 | 92.8±0.4 |
| 120         | 99.2±0.7 | 89.6±0.5 |

**Table 4: Polydispersibility index of Losartan SMEDDS formulations**

| Formulation code | PDI   |
|------------------|-------|
| C1               | 0.123 |
| C2               | 0.083 |
| C3               | 0.236 |
| C4               | 0.208 |

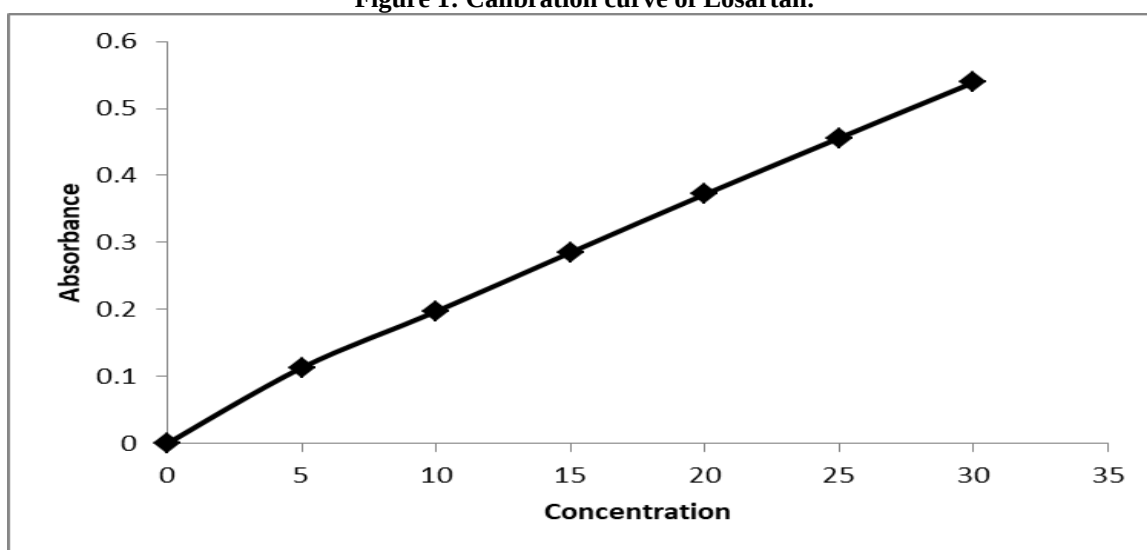
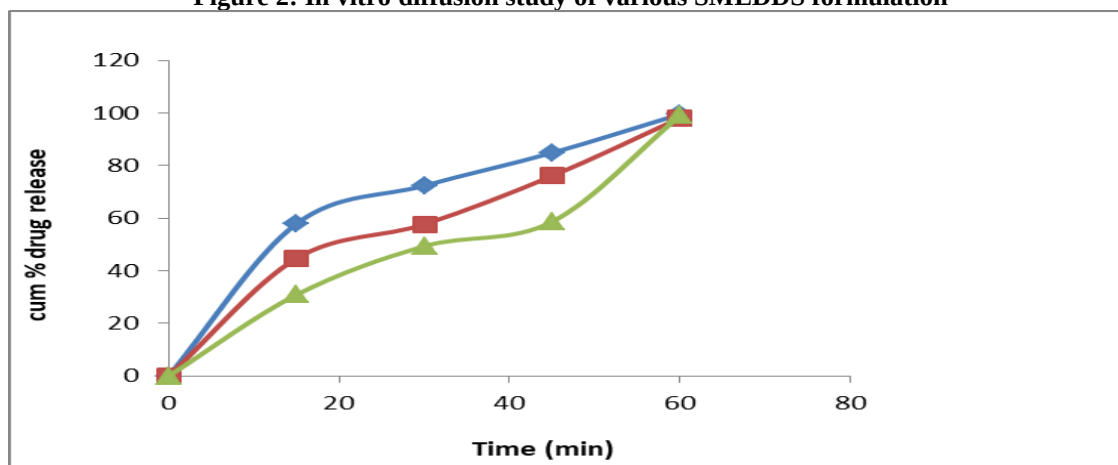
**Table 5: Comparison of In-vitro drug release of various SMEDDS formulations**

| Time (min) | C1   | C2    | C3    | C4    |
|------------|------|-------|-------|-------|
| 15         | 57.9 | 44.69 | 30.86 | 40.17 |

|    |       |       |       |       |
|----|-------|-------|-------|-------|
| 30 | 72.38 | 57.68 | 49.37 | 67.29 |
| 45 | 84.87 | 76.09 | 58.68 | 81.05 |
| 60 | 99.57 | 98.13 | 99.10 | 94.84 |

**Table 6: Stability data of C4 and Marketed formulation for % Drug content**

| Period (days) | 25°C  |       | 40°C  |       |
|---------------|-------|-------|-------|-------|
|               | C4    | M     | C4    | M     |
| 15            | 99.03 | 98.36 | 98.75 | 98.36 |
| 30            | 98.48 | 98.02 | 96.26 | 89.23 |
| 45            | 97.67 | 96.89 | 92.63 | 81.63 |
| 60            | 96.16 | 96.63 | 87.85 | 76.73 |
| 90            | 95.77 | 95.60 | 82.45 | 70.26 |
| 120           | 95.05 | 94.41 | 75.76 | 68.74 |

**Figure 1: Calibration curve of Losartan.****Figure 2: In vitro diffusion study of various SMEDDS formulation*****In- vitro* diffusion study:**

It is valuable to predict the behavior of a formulation with respect to drug transport across membranes with the help of in-vitro diffusion. In-vitro

evaluation techniques can be used to determine physicochemical parameters about formulations, including flux, partition coefficient, and diffusion coefficient. In comparison to all liquid SMEDDS

formulations, formulation C4 showed the highest rate of release, 99%. Therefore, we considered this formulation to be the most suitable liquid SMEDDS formulation.

A C4 formulation releases more than 50% of the drug within 15 minutes, compared to a conventional capsule formulation, which releases 35 to 40%, and a suspension formulation, which releases less than 10%. Aqueous contact with the dialysis bag is required to form self-microemulsion SMEDDS. Because of its high viscosity, the blend was unable to diffuse through the membrane and did not form a microemulsion, preventing drug release. Due to this, SMEDDS was diluted with water before being infused into the dialysis bag. Aqueous phase consisted of water and microglobules of microemulsion. A microemulsion particle's size is so small that it easily passes through a dialysis membrane.

As oil at the same wavelength as the drug interfered with the UV method for formulation, this interference did not occur once the drug was released through the dialysis bag. This indicates that oil globules are incapable of diffusing through membranes, and only drugs are able to penetrate those membranes. According to the in-vitro study, SMEDDS greatly enhanced Losartan release.

According to the results, formulation C4 has the highest release rate at 60 minutes, i.e. 99 out of all formulations. This batch is therefore the most optimized for liquid Losartan SMEDDS formulations.

#### Stability Studies:

Based on the results of all characterization points, the results of formulation C4 were compared with the conventional Losartan capsule. According to these values, formulation C4 does not exhibit any significant differences in particle size, zeta potential, or particle density index after the stability study. A stability study found that the particle size of C4 after three months was 10.19 nm, which was not significantly different from its initial size of 10.17 nm. PDIs initially were 0.096, and final PDIs were 0.102, according to the stability study. During stability studies, we found that the zeta potential had changed from -26 mV to -24 mV. Therefore, all the excipients have similar particle sizes and therefore form a stable microemulsion. Zeta potential plays an essential role in determining microemulsion stability. Zeta potential results in electrostatic attraction between two droplets. An electrolyte concentration in the continuous

phase below a certain threshold will lead to electric double layer repulsion that stabilizes the microemulsion. In the presence of a negative force, there is a negative potential between droplets.

A vanderwaals attraction occurs when two particles approach each other, resulting in flocculation and an increase in droplet size. The viscosity of the system increased proportionately to the size of the droplets. Oil droplets additionally reduced the amount of UV light transmitted, and thereby the transmittance percentage. It is specified in the ICH guidelines that stability conditions can be determined by determining a specific zone. Over a period of three months, two conditions were used in this study, namely 25 °C and 40 °C. Results suggest formulation C4 to be the most stable formulation. On the basis of T percentage and drug content, two formulations were compared. During the 3 month period, the amount of drug in C4 decreased by 3%. At 25 °C, the amount of drug decreased by 4%.

#### CONCLUSION

As compared to other oils, Capryol 90 is the most soluble in captopril as compared to others, whereas losartan was found to be the least soluble in water by being able to dissolve up to  $0.09 \pm 0.01$  mg/ml. Therefore, Capryol 90 was selected as the oil phase for the formulation. The prepared SMEDDS formulations are observed to be clear when diluted and are classified. There was a poor microemulsion when the cosurfactant concentration was higher than the surfactant concentration in the microemulsion. Considering that SMEDDS contain a higher concentration of oil, it may be more likely that there will be high concentrations of losartan that are dissolved and incorporated into the system as a result of the higher oil concentration. It was observed that all formulations had a viscosity below 0.8 cp, which indicates that SMEDDS form o/w microemulsions. There was evidence obtained by the formulation that the average particle size of the particles would be at least 10.2 nanometers on average. Several stability studies have been conducted with formulation C4 and they have demonstrated that the formulation has a higher stability profile than the conventional capsules of losartan. Bioavailability of losartan may be enhanced by the optimal formulation of losartan SMEDDS.

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