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Self Nano Emulsifying Drug Delivery System : Formulation And In Vitro Characterization

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Introduction :

Self-emulsifying drug delivery systems (SEDDS) are isotropic mixtures of drug, lipids and surfactants, usually with one or more hydrophilic cosolvents or coemulsifiers . Upon mild agitation followed by dilution with aqueous media, these systems can form fine (oil in water) emulsion instantaneously.

- **Types of Self-emulsifying drug delivery systems**

1) **Self nano emulsifying drug delivery system**
2) **Self micro emulsifying system**

1) Self-nanoemulsifying drug delivery systems (SNEDDS) are anhydrous homogenous liquid mixtures consisting of oil, surfactant, drug and coemulsifier or solubilizer, which spontaneously form oil-in-water nanoemulsion of approximately 200 nm or less in size upon dilution with water under gentle stirring.

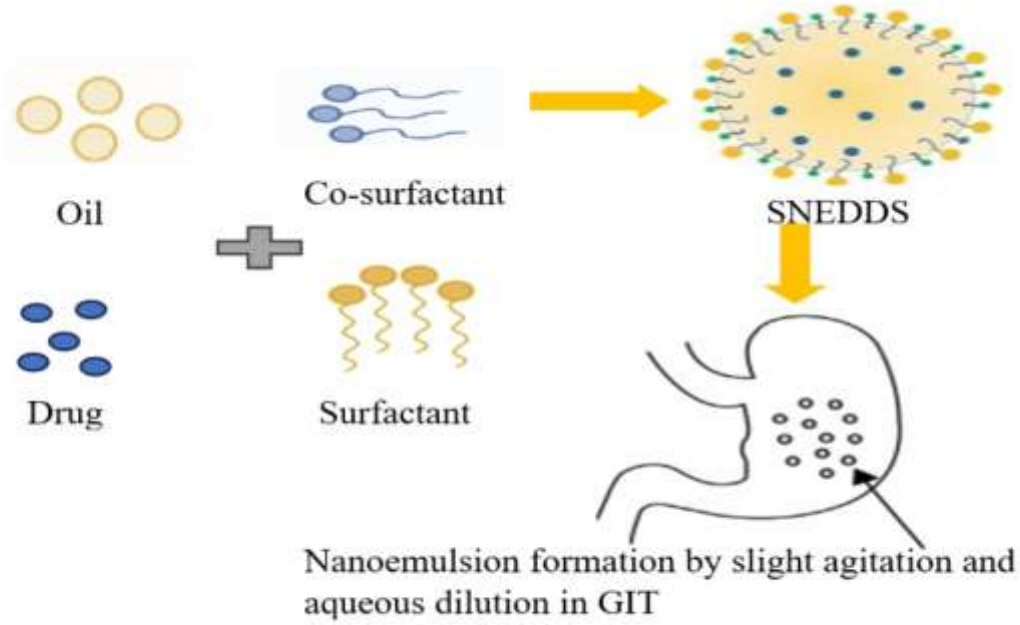


Fig. 1: Mechanism of SNEDDS

Approaches of self nano emulsifying drug delivery system :

Self-emulsifying drug delivery systems (SEDDS) are mixtures of oils and surfactants, ideally isotropic, sometimes including co-solvents, which emulsify under conditions of gentle agitation, similar to those which would be encountered in the gastrointestinal tract.

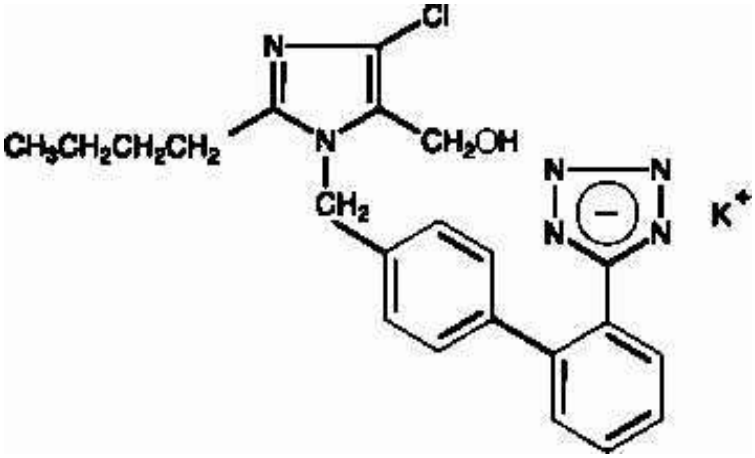
- **Methodology**
- **Solubility studies**
- **Screening of oil**
- **Preparation of self nano emulsifying system**

NEED OF STUDY :

- **Self-emulsifying drug delivery systems (SEDDS) are a proven method for poorly soluble substances works by increasing the dissolution rate.**
- **SEDDS and isotropic mixtures, are composed of oils, surfactants, and occasionally cosolvents. Self-nanoemulsifying drug delivery systems (SNEDDS) are most commonly used lipid-based drug delivery systems for bioavailability enhancement.**
- **Helps in the effective transportation of active substances through a semipermeable membrane, and due to the large surface area, penetration increases in the emulsion system. Besides preventing droplet flocculation, nano emulsions' small globule size additionally avoids larger droplet flocculation.**

Drug profile of losartan potassium :

- **Losartan potassium**



A. IUPAC name :2-butyl-4-chloro-1- [p- (o-1H-tetrazol-5-ylphenyl) benzyl]imidazole-5-methanol

B. Structural formula :

C. Molecular formula : C22H23CIKN6O

D. Molecular weight : 422.9

E. Physicochemical properties :

Pka of 4.9, PH dependent solubility [12] , Losartan has been shown to degrade under acidic conditions, under thermal stressing at 70 °C, by oxidation and is also photodegradable.

F. Category: Angiotensin receptor antagonist.

G. Dose : 30-50 mg

H. Pharmacokinetics : Absorption Losartan potassium. It is well absorbed orally

Bioavailability 33%, Plasma half life 1.5-2.5 hours,

I. Indications :

- **Hypertension (High blood pressure)**
- **Heart failure**
- **Nephropathy in type ll diabetic patients**

Experimental Work :

- **Preformulation study**
- **Physical appearance and melting.**
- **Fourier Transmission infrared (FIR) studies of losartan potassium**
- **Construction of ternary phase Diagram**

The relation between composition of a mixture and its phase behavior can be known with construction of phase diagram. Pseudo ternary phase diagrams were developed by water titration method against oil, surfactant and co-surfactant. The weight of surfactant and co-surfactant was differed as 1:1 and 1:2 respectively. Oil and surfactant/co-surfactant mixture mixed thoroughly in various weight ratios (1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2 and 9:1) respectively. Water was added slowly drop by drop wing burette under vigorous stirring at 37°C until the mixture was obtained clear through which the concentrations of the components were rrecorded.

Solubility studies of drug :

- **The most important criterion for the screening of components for emulsion is the solubility of poorly soluble drug rug in oils, surfactants 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 vertexing. The mixture vials were then kept at 25±10°C 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 (El double beam UV-VIS spectrophotometer UV/Visible model 1372) at 251 nm.**

- **Preparation of losartan potassium loaded Self nano emulsifying Drug delivery system :**

  Preparation of self nanoemulsifying system: A series of SNEDDS were prepared using oleic acid as the oil, Tween 80 as surfactant and polyethylene glycol as the co-surfactant. In all the formulations, the amount of Losartan Potassium was kept constant. Accurately weighed losartan potassium was placed in beaker and oil, surfactant, and co-surfactant were added. The components were mixed by gentle stirring with magnetic stirrer and the resulting mixture was heated at 40°C, until the drug was completely dissolved. The homogenous mixture was stored at room temperature until further use.

- **Emulsification time**
- **Stability study**
- **Preparation of pellets :**
- **The pellets were produced by the following processes: initially the resulted Solid SNEDDS was completely adsorbed to form a fine mixture. Then, the adsorbed mixture was blended with other components (MCC) for 5 minutes. Add drops of PVP 2% were added until a mass with suitable consistency was obtained for extrusion. The wet mass was loaded to screw feed extruder with a die of 1mm thickness and 1 mm diameter holes. The extrudates were spheronized for 5 minutes, at 1000 rpm on a spheronizer. The produced pellets were then dried for 15 h at 40 °C in an oven drier. The pellets were stored in sealed bags. Formulation of the pellets was selected from the ternary phase diagram**
- **In Ternary phase diagram Tween 80, PEG 400, Oleic acid selected excipients having 1:2 ratio gives more emulsion formation region, formulation was selected according to 1:2 ratio. The composition of SE pellets is shown in Table.**

Formulation of self emulsifying pellets :

Ingredients	Quality
Losartan Potassium	300mg
Oleic Acid	1 ml
Tween 80	2 ml
PEG 400	2 ml
Aerosil 200	2.5 gm
Microcrystalline Cellulose	2.5 gm
PVP solution (2%)	QS

Table 1: formulation of snedds pellets

Result and Discussion :

Sr. No.	Character	Inference
1	Nature	Amorphous
2	Colour	White
3	Odour	Ouderless
4	Taste	Slightly better

Table 2: Physical characteristics of drug

Solubility studies of drug :

Sr.No.	Name of Vehicles	Solubility found (mg/ml)
1	Oleic acid	80.5
2	Tween 80	82.9
3	PEG-400	78.2
4	Caster oil	67.1
5	Span 80	70.9
6.	PEG 200	60.9
7.	Soyabean Oil	57.6

Table 7 : Solubility of drug

CALIBRATION TABLE :

Sr. No	Concentration	Absorbance
0	00ug/ml	0.0000
1	2 ug/ml	0.0519
2	4 ug/ml	0.1295
3	6 ug/ml	0.2134
4	8 ug/ml	0.2889
5	10 ug/ml	0.3791
6	12 ug/ml	0.4672

Table 3: calibration table

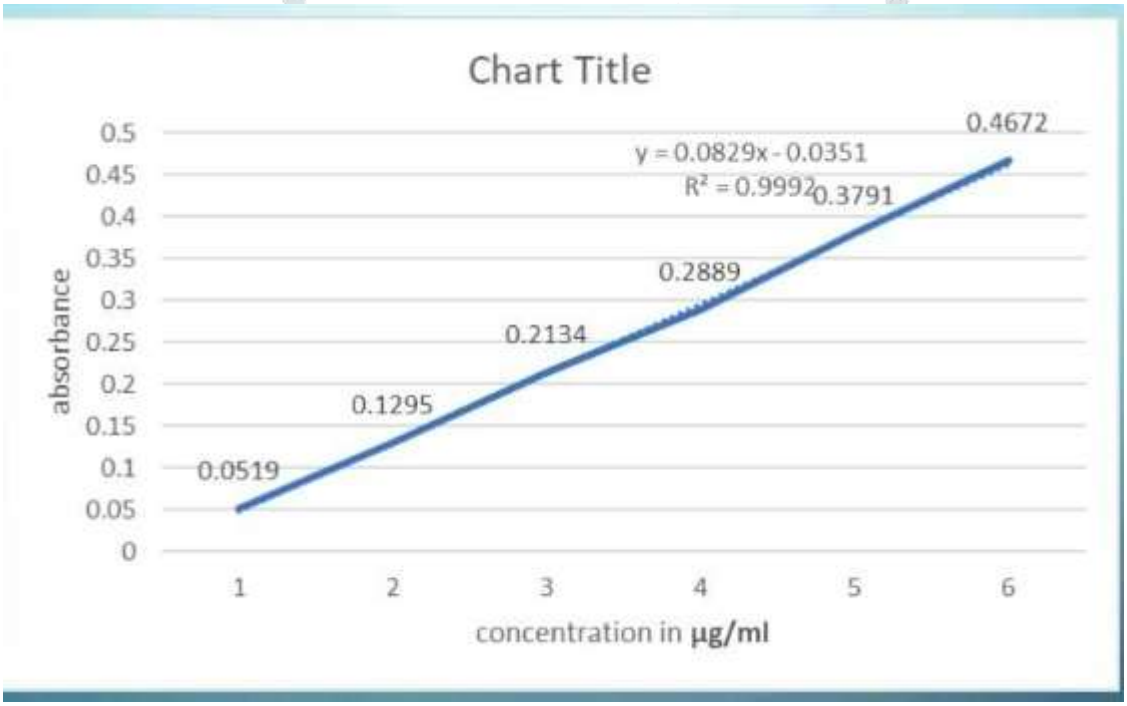


Fig : 2 Calibration curve

Calibration curve with losartan potassium drug having Correlation coefficient is 0.999 hence it shows linearity and slope is 0.0829 and intercept is0. 3791.

Pseudo ternary phase diagram :

To determine optimum concentration of oil, surfactant and co-surfactant, pseudo ternary phase diagrams were constructed using ternary plot software. Self micro-emulsifying performance of SME mixture was assessed from their ternary phase diagrams and time taken to produce a fine nanoemulsion. Only certain combinations of oil, surfactant and a cosurfactant in a certain composition range will produce a fine nanoemulsion upon aqueous dilution. To check emulsification efficiency of SME mixtures, test for emulsification was performed on all eight combinations and the resultant dispersions were visually assessed. Resulting dispersions either formed a clear nanoemulsion, a slightly turbid emulsion or a milky emulsion which immediately phase separated.

Ratio	Smix	Oil	Water
9:1	9.43 %	84.9 %	5.67 %
8:2	19.04 %	76.19 %	4.77 %
7:3	28.84 %	67.30 %	3.86 %
6:4	37.73 %	56.60 %	5.66 %
5:5	46.29 %	46.29 %	7.42 %
4:6	52.63 %	35.08 %	12.29 %
3:7	62..5 %	26.78 %	10.72 %
2:8	73.39 %	18.34 %	8.27 %
1:9	78.26 %	8.69 %	13.05 %

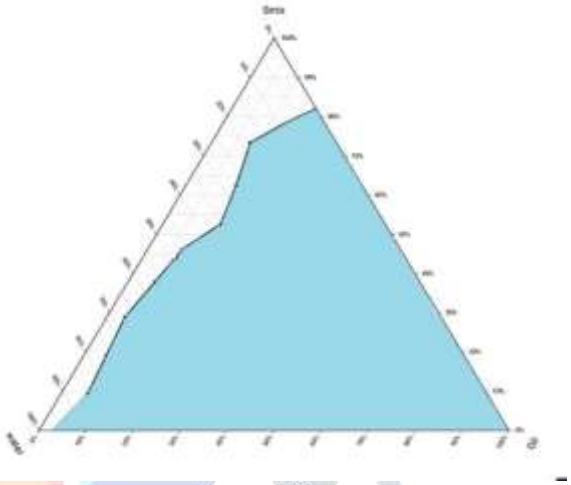


Fig 1 : Ternary phase diagram with oleic acid, Tween 80 : PEG 400 (1:1)

Ratio	Oil:Smix	Grade A	Grade B	Grade C
	1:9	_	_	✓
	2:8	✓	_	_
	3:7	_	✓	_
	4:6	_	✓	_
1:1	5:5	_	✓	_
	6:4	_	✓	_
	7:3	_	✓	_
	8:2	_	✓	_
	9:1	_	✓	_

Table 5 : Visual observation of snedds mixture to completely self emulsify surfectant cosurfectant (1:1) ✔ idicates emulsion form & _ indicates emulsion is not form.

Grade A : Foam forming faint yellow colour selfnano emulsion form

Grade B : Milky white micro emulsion form

Grade c : Yellow colour emulsion form

Ratio	Smix	Oil	Water
9:1	73.1	8%	8.1
8:2	76.1	19	19
7:3	64.8	27.7	7.5
6:4	57.6	38.4	4
5:5	46.29	46.29	7.42
6:4	37.7	56.6	5.7
7:3	29.1	67.9	3
8:2	19	76.1	4.9
9:1	9.6	86.5	3.9

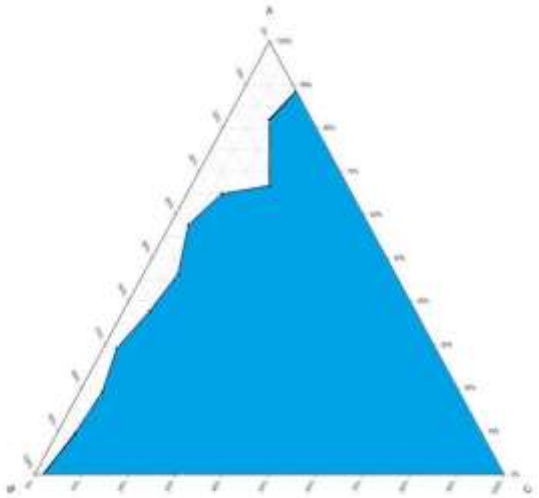


Fig 2 : Ternary phase diagram with oleic acid , Tween 80 : PEG 400 (1:2)

Ratio	Oil:Smix	Grade A	Grade B	Grade C
	1:9	–	✓	–
	2:8	–	–	✓
	3:7	✓	–	–
	4:6	–	–	✓
1:2	5:5	–	✓	–
	6:4	–	✓	–
	7:3	–	–	✓
	8:2	–	✓	–
	9:1	–	✓	–

Table 6 : visual observation of snedds mixture to completely self emulsify surfactant Cosurfactant (1:2) sign (-)indicates emulsion didn't form, (✔) indicates emulsion form.

Grade A : Foam forming faint yellow colour self nano-emulsion form

Grade B : Milky white micro emulsion form

Grade c : Yellow Colour emulsion form

FTIR of SNEDDS pellets of losartan potassium :

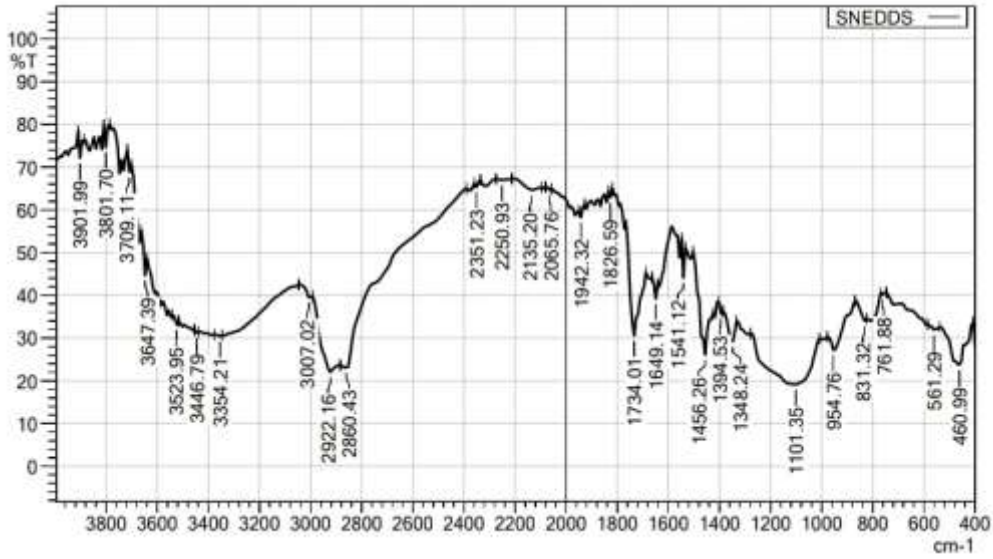


Fig 3 : FTIR of snedds pellets of losartan potassium

FTIR of pure losartan potassium drug :

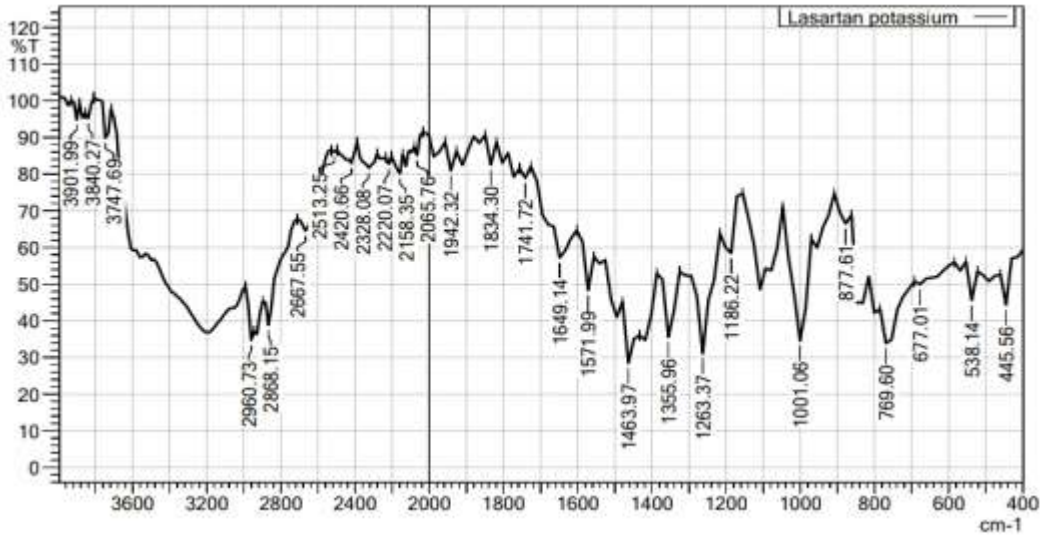


Fig 4 : FTIR of snedds pellets of losartan potassium

Globule size analysis of SNEDDS :

Hydrodynamic diameter	**137.20 nm**
Polydispersity index	**0.266**
Diffusion coefficient	**115.5 µm²/s**
Transmittance	**131.9%**
Mean intensity	**33.9 kcounts/s**
Absolute intensity	**33.9 kcounts/s**
Intercept g12	**0.2320**
Baseline	**1.155**

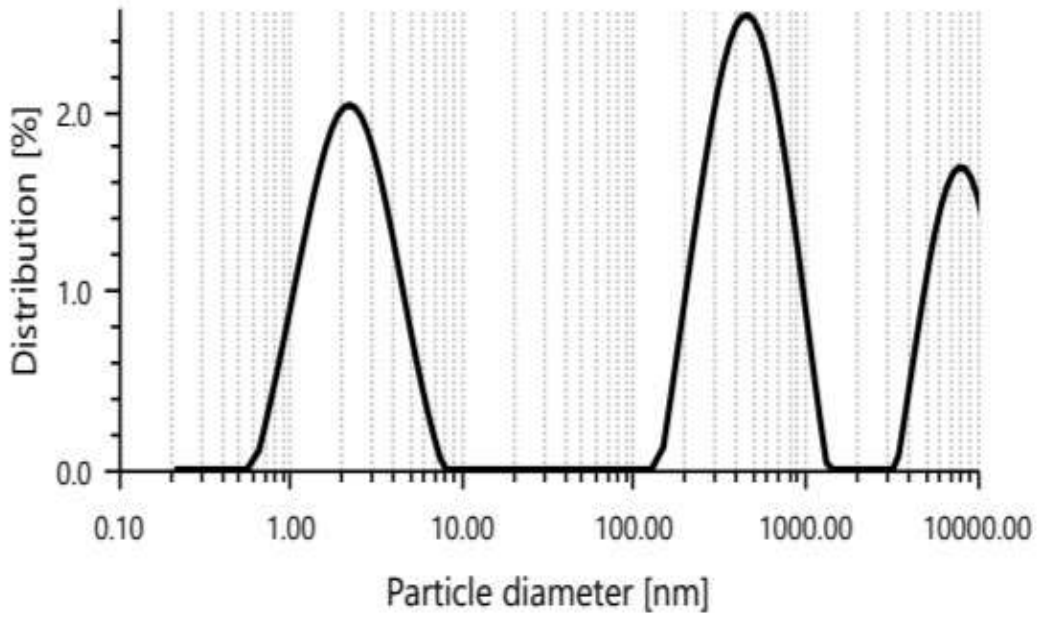


Fig 5 : Globule size analysis

Evaluation of self nano emulsifying pellets :

- **Mean zeta potential** **0.4 mv**
- **Standard deviation** **0.9 mv**
- **Distribution peak** **0.0mv**
- **Electrophoretic Mobility** **-0. 0578 µm*cm/Vs**
- **Mean intensity** **638.4 kcounts/s**
- **Filter opical density** **1.4104**
- **Conductivity** **0.419 mS/cmTransmittance 175.3%**

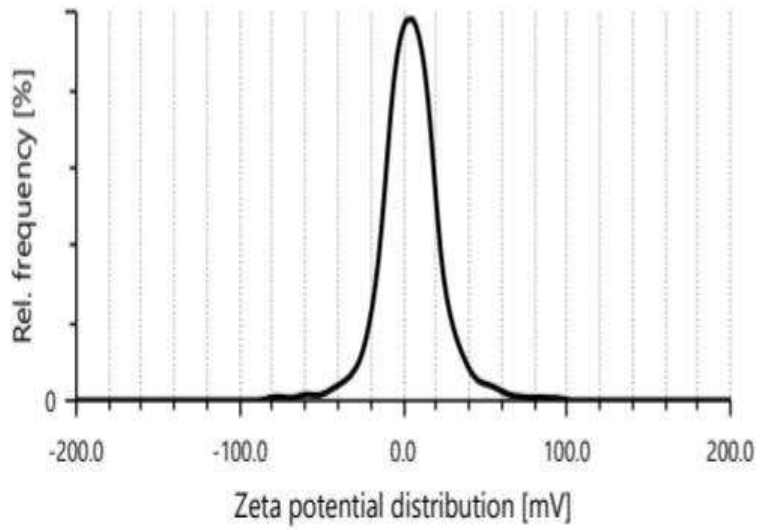


Fig 6 : Zeta Potential

Stability study and emulsification time :

- **Stability study :-**

  Emulsion is stable after 60 days at 40c no colour change and disperse content was not found

- **Emulsification time :-**

  It required about 10 to 15 second to emulsify.

Evaluation of self nano emulsifying pellets :

Parameters	Batch
Bulk density (g/cm3)	0.5128
Tap density g/cm3)	0.5882
Carr's Index	7.28
Hausner's Ratio	1.1470
Friability (%w/w)	5
Drug content	95.29
Angle of repose	32.9

Table 8 : Evaluation of self nano emulsifying pellets

Conclusion :

The Self-Emulsifying drug delivery systems are promising approach for the formulation of poorly aqueous soluble drugs The oral delivery of hydrophobic drugs can be made possible by SEDDSs, which shows the improved solubility and bioavailability.

The present study aims towards the formulation and evaluation of Self- Emulsifying drug delivery system of Losartan potassium. The development of SEDDS which were corporated into pellets, which increases solubility and permeability of Losartan potassium.

Losartan potassium is a medication in the angiotensin receptor antagonist class that is used for treating hypertension, kidney damage due to type 2 Diabetes. These poorly water-soluble drug falls under BCS class II, is formulated into SEDDS which improves solubility and bioavailability of the drug.

The preformulation study of Losartan potassium was performed. Total eight Self-Emulsifying mixtures comprising of components were evaluated. The Tween 80- PEG 400 – Oleic acid mixture possessed the largest SME region in the phase diagrams and took the least time to nano-emulsion. The Solubility of the drug Losartan potassium was determined in selected oils, surfactant and co-surfactant Types of oil, surfactant and cosurfactant concentration play a vital role in SEDDS formation. Based on the Solubility studies Oleic acid was selected as oil phase, Tween 80 was selected as the surfactant and PEG400 was selected as cosurfactant The Pseudoternary phase diagram was constructed in absence of drug to identify the Self-Emulsifying regions and to optimize the concentration of oil, surfactant and co- surfactant in SEDDS by water titration method. In Ternary phase diagram 2:8 ratio gives more emulsion formation region, formulation was selected according to 2:8 ratio.

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