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DESIGN, DEVELOPMENT AND EVALUATION OF NITRENDIPINE LOADED SELF NANOEMULSIFYING DRUG DELIVERY SYSTEM

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ABSTRACT:-

The aim of this work was to improve the in-vitro dissolution of Nitrendipine through development of self nanoemulsifying capsules. Nitrendipine is an anti-hypertensive agent used to treat mild to moderate Hypertension. It has poor oral bioavailability so self nanoemulsifying drug delivery of Nitrendipine enhances its bioavailabilty. For the construction of pseudo ternary phase diagram the oil phase (Ethyl oleate/ Olive oil/ Castor oil), surfactant, co-surfactant (Tween 80 and PEG 400) and aqueous phase (Distilled water) was selected. Surfactant and co-surfactant (Smix) were mixed at (3:1) ratio and prepared phase diagram. The Liquid-SNEDDS (F1-F3) were prepared by using different ratios of Ethyl oleate (oil phase), Tween 80 (Surfactant) and PEG 400 (Co-surfactant) based on Ternary Phase Diagram. The prepared formulation will be characterized for several parameters such as physical appearance, pH, Scanning Electron Microscopy, Drug content, Drug entrapment efficiency, *in vitro* drug release, and stability studies. At the end it can be concluded that the optimized formula were able to introduce Nitrendipine successfully in SNEDDS to enhance the oral bioavailability of Nitrendipine.

KEYWORDS:-

Nanoemulsion, Nitendipine, Self nanoemulsifying drug delivery system(SNEDDS), Ternary Phase Diagram, Surfactants.

1. INTRODUCTION:-

1.1 Solid Self-Nanoemulsifying Drug Delivery System:-

Self- Nanoemulsifying Drug Delivery System (SNEDDS) are anhydrous form of nanoemulsion. They are the preconcentrates of nanoemulsion. SNEDDS are isotropic mixture of surfactants, cosurfactants and oils (natural or synthetic) [1]. SNEDDS are emulsifying systems used to enhance the solubility of BCS class II and BCS class IV

drugs. SNEDDS are translucent and thermodynamically stable oil in water or water in oil nanoemulsions that are prepared using medium chain triglyceride oils and surfactants and further stabilized using co-surfactants [2].

1.1.1 Structure of SNEDDS:-

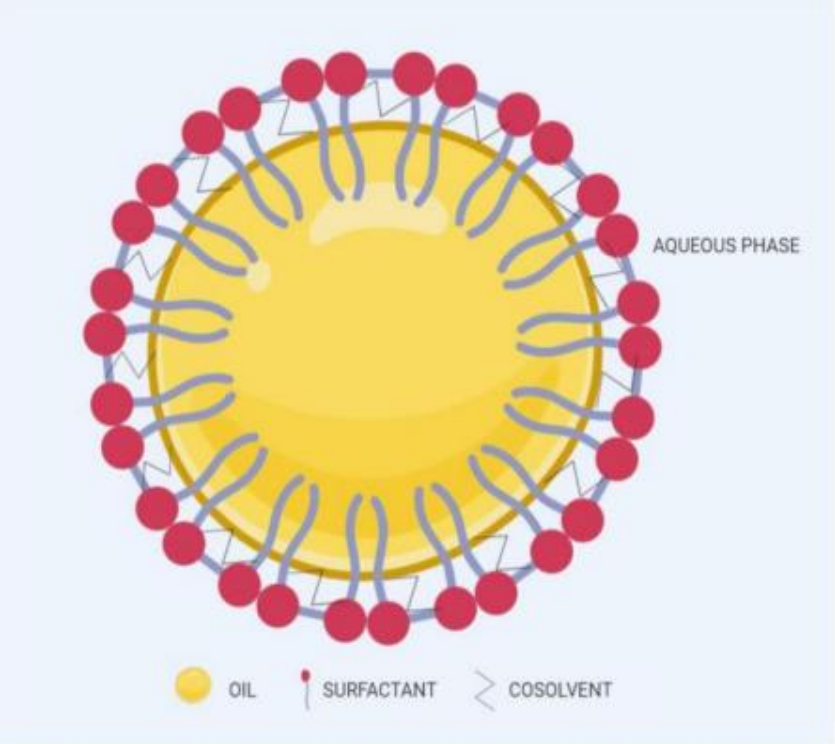

Figure 1.1 Typical structure of SNEDDS [3]

1.1.2 Advantages of SNEDDS:-

- Improved Pharmacokinetics: SNEDDS are useful in improving the pharmacokinetics of the drugs incorporated and helps in reducing the dosage frequency [4]
- Patient Compliance: Reducing dosage frequency directly increases the patient compliance
- Drug payload: SNEDDS has higher drug payload when compared to other delivery systems
- Ease of manufacturing: SNEDDS are easier to manufacture and are economical
- Stable formulations: SNEDDS are thermodynamically stable formulations and are easier to store and transport
- Protection from gastric environment: SNEDDS are formulations in which the drugs are dispersed in oil phase or aqueous phase and hence are protected from gastric environment with acidic pH [5]
- Lower gastric irritation: SNEDDS are formulations in which the drugs are dispersed in oil phase and hence have lesser contact with the gastrointestinal walls and reduces gastric irritation caused by drug.

1.1.3 Mechanism of action:-

When SNEDDS are ingested, the stomach's gastric motions agitate the formulation and instantly transform it into a nanoemulsion with particles smaller than 200 nm.

The emulsion's nano-range enables the medicine to enter the GIT quickly for absorption. Surfactants and the oil phase increase the interfacial area, improve medication solubility, and increase permeability [6].

1.1.4 Components of SNEDDS:-

The SNEDDS are mainly composed of API, surfactants, co-surfactants, oils and co-solvents.

- **Active Pharmaceutical Ingredients:** Drugs that are lipophilic or fall within BCS Classes II and IV make suitable candidates for SNEDDS development. Drugs that have a log P value greater than 5 are lipophilic drugs and are ideal SNEDDS candidates.
- **Surfactants:** Surfactants are ionized or de-ionized molecules that lower the interfacial tension and increase the interfacial area between two phases. Depending on the desired droplet size of the nanoemulsion and the administration route, the surfactants are selected.
- **Co-Surfactants:-**Co-surfactants are used in combination with surfactants to improve the solubility of drugs that aren't very soluble in water. In SNEDDS, co-surfactants are introduced to lower interfacial tension, enhance surface area, and promote spontaneous nanoemulsion production. For the formulation of SNEDDS, co-surfactants with HLB values between 10 and 14 are typically chosen. Hexanol, Pentanol, Octanol, Polyethylene Glycols, Castor Oil, etc. are some examples [7].
- **Co-Solvent:-** In the formulation of SNEDDS, normally greater concentrations of surfactants are used; thus, co-solvents are added in the formulation to enhance the solubility of surfactant. Ethanol, polyethylene glycol, and propylene glycol are a few examples.
- **Oils:-** Oils are required in the formulation of SNEDDS for the self-emulsification and solubility of drugs that are poorly soluble in water. Although edible oils are not included in the formulation, the oils that are added to it can be either natural or synthetic. Olive oil, oleic oil, mineral oil, medium- and long-chain triglycerides, soyabean oil, castor oil, sesame oil, and others are some examples.

1.2 NITRENDIPINE:-

Nitrendipine is an anti-hypertensive agent used to treat mild to moderate Hypertension. Nitrendipine, an oral dihydropyridine calcium channel blocker or antagonist, is used to prevent calcium from moving through slow channels in the smooth muscles of the heart and blood vessels. It causes peripheral vasodilation, which lowers blood pressure. Nitrendipine is used to treat mild and moderate hypertension [8-10].

1.2.1 Mechanism of action:-

Nitrendipine acts by blocking or deforming the calcium channel by inhibiting the ion-gated channels or by interfering the release of calcium from Sarcoplasmic Reticulum. It further inhibits the influx of calcium ions across the myocardial and vascular smooth muscles. The decrease in calcium ions inhibits the contraction of smooth

muscles, causing dilation of coronary and systemic arteries, increased oxygen delivery, decreased peripheral resistance, decreased systemic blood pressure, and decreased after load [10].

1.3 EXCIPIENTS:-

1.3.1 Ethyl Oleate:-

Ethyl oleate is a fatty acid ester prepared by condensation of ethanol and Oleic acid. It is a pharmaceutical industry solvent and an FDA-approved food ingredient. "Oleic" refers to something that is connected to or derived from olive or oil. It is an odourless, colourless oil, but occasionally oxidation causes the colour to fade to a pale yellow.

1.3.2 Olive Oil:-

Olive oil is a fixed oil used extensively in pharmaceutical and cosmetic industries. It is obtained from the fruit Olea europaea. Olive oil is an oleaginous excipient used in oral, topical and parenteral solutions [11].

1.3.3 PEG 400:-

Ethylene oxide and water are condensed to create polyethylene glycol (PEG) 400. Because PEG 400 is hydrophilic by nature, it can help make medications that aren't very soluble more soluble.

1.3.4 TWEEN 80:-

Tween 80 is a non-ionic surfactant derived from polyethoxylated sorbitan and oleic acid.

2. MATERIAL AND METHODS:

Nitrendipine was obtained from Anant Pharmaceuticals Pvt. Ltd. Ethyl Oleate were obtained from S.D. Fine chemicals Ltd, India. Olive oil, Castor oil, Tween 80, PEG 400, Ethanol, Phosphate Buffer, Sodium Chloride, Sodium hydroxide, Disodium hydrogen phosphate and Hydrochloride acid were also obtained from from S.D. Fine chemicals Ltd, India.

2.1. Evaluation of Raw Materials:

According to the formal processes outlined in the relevant monographs, drug and other excipient identification and standardization were completed.

2.2 Preparation of SNEDDS:-

2.2.1 Construction of pseudo ternary phase diagram:-

The oil phase (Ethyl oleate/ Olive oil/ Castor oil), surfactant, co-surfactant (Tween 80 and PEG 400), and aqueous phase (Distilled water) were selected based on solubility tests and drug excipient compatibility studies. A phase diagram was created when the surfactant and co-surfactant (S_{mix}) were blended in a 3:1 ratio. For phase diagram, oil

and Smix were mixed thoroughly at different mass ratios (1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, 9:1) in different glass vials as depicted in table 2.1.

Table 2.1 Aqueous Titration of oil, surfactant and co-surfactant (Smix 3:1)

S. No.	Formulation	Oil/S_{mix} (ratio)	Oil	S_{mix}	Water	Total	% w/w of components		
							Oil	S_{mix}	Water
1	F1	1:9	50	450	386	886	5.64	50.8	43.5
2	F2	2:8	100	400	354	854	11.7	46.83	41.45
3	F3	3:7	150	350	329	829	18.09	42.21	39.68
4	F4	4:6	200	300	366	866	23.09	34.64	42.26
5	F5	5:5	250	250	411	911	27.44	27.44	45.11
6	F6	6:4	300	200	392	892	33.63	22.42	43.94
7	F7	7:3	350	150	247	747	46.85	20.08	33.06
8	F8	8:2	400	100	209	709	56.41	14.1	29.4
9	F9	9:1	450	50	311	811	55.4	6.16	38.34

2.2.2 Formulation of Liquid-SNEDDS:-

Based on the Ternary Phase Diagram, L-SNEDDS were created using various ratios of Ethyl oleate (oil phase), Tween 80 (surfactant), and PEG 400 (co-surfactant). The three formulations (F1-F3) were created by dissolving 150mg of the medication (Nitrendipine) in Ethyl oleate, Tween 80, and PEG 400.The mixture was then heated to 40°C in a water bath and vortexed until it was translucent and clear. For future use, all formulations were maintained at room temperature.

3 RESULT AND DISCUSSION:-

3.1 Evaluation of L-SEDDS:-

3.1.1 Determination of Globule size:-

Photon correlation spectroscopy using dynamic light scattering was used to measure the average globule size of L-SNEDDS. The globular size of all formulations was in the nano range and shown in table 3.1.

3.1.2 Thermal Stability Studies:-

The Heating cooling cycle and freeze thaw stress cycle showed no phase separation or precipitation in all three formulations indicating stability of formulations under effect of temperature. The results of thermal stability studies are depicted in table 3.1.

3.1.3 Self-Emulsifying Efficiency Test- Visual Assessment Test:-

The emulsification time was visually determined by monitoring the appearance of nanoemulsion and the disappearance of SNEDDS. When water is added to the optimum SNEDDS formulation, it should disperse completely and quickly under continuous stirring at 37°C. The results showed a self-emulsification time of 35-48 seconds. The formulations demonstrated full, simple, and quick emulsification. The results are depicted in table 3.1.

Table 3.1 Characterization of L-SNEDDS (F1-F3)

S. No.	Formulation	Globule size (nm)	Thermal Stability Studies	Self-Emulsification Time (sec)	pH
1	F1	555.6 ± 0.2	No phase separation/ Precipitation	36	5.2
2	F2	762.3 ± 0.1	No phase separation/ Precipitation	32	5.3
3	F3	1350 ± 0.5	No phase separation/ Precipitation	25	5.7

3.1.4 Phase Separation and Stability Test:

The L-SEEDS formulations were checked visually for any evidence of phase separation. The results showed no phase separation and hence depicted the stability of the L-SEDDS formulation.

3.1.5 pH Determination:

The pH of L-SNEDDS formulation was determined using a digital pH meter at 25 ± 0.5°C. The pHof the formulations was found to be in the range 5.2-5.7 which indicates that it can be used on skin and will not cause any form of irritation or irritability.

3.1.6 Drug Loading Efficiency:

UV spectrophotometry was used to measure the drug loading efficiency. The% drug loading efficiency was determined and found to be between 78.4 and 83.2%. The results for all formulations are depicted in figure 3.1.

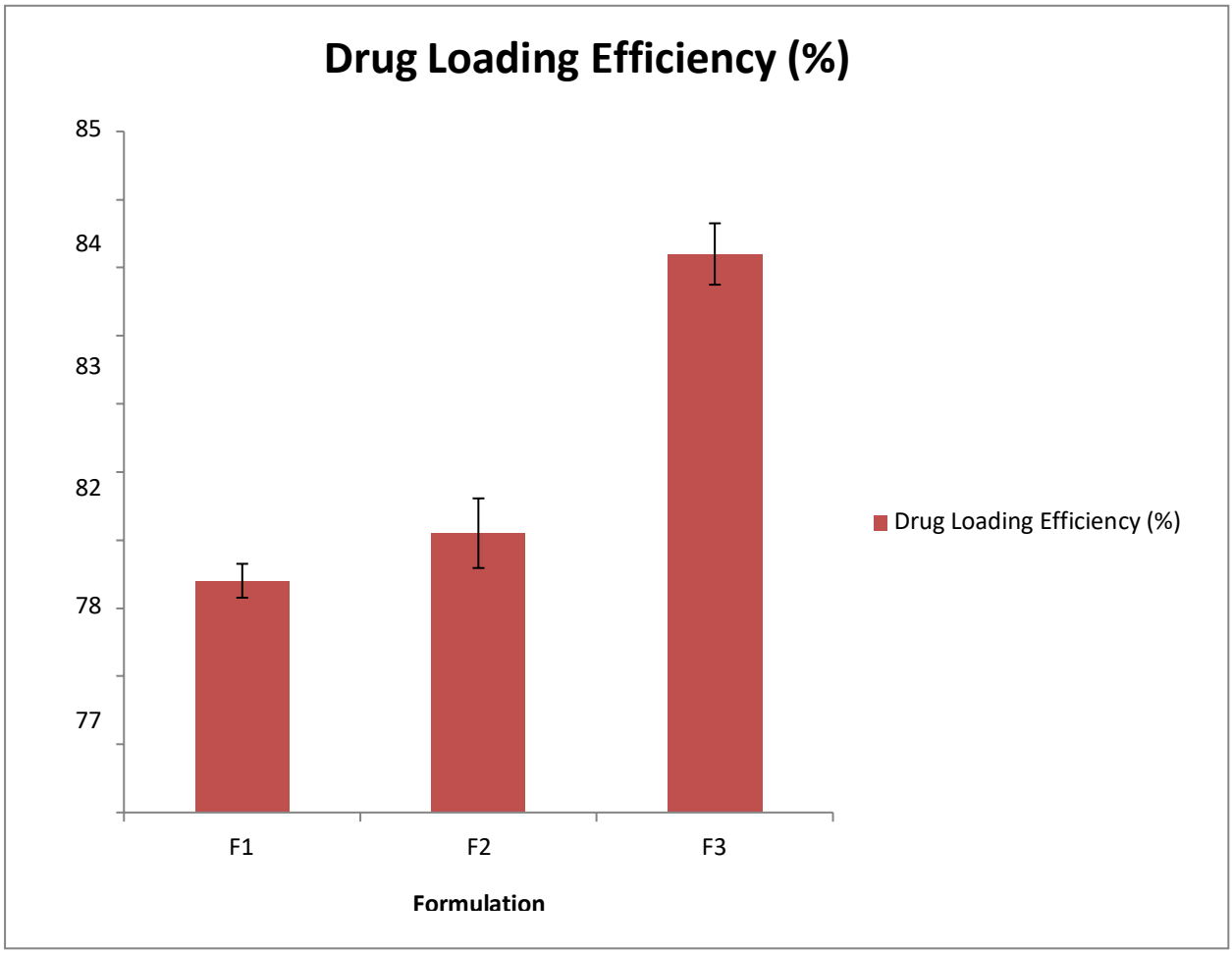

Figure 3.1 Drug Loading Efficiency (%) of L-SNEDDS (F1-F3)

3.1.7 In-Vitro Drug Release Studies

The USP II dissolution test apparatus was used for the *in-vitro* drug release studies. The L SNEDDS formulations showed drug release between 86.5 to 93.7% within 2hrs. The *in vitro* drug release pattern seemed to be dependent

on the globule size of L-SNEDDS. The globule size related inversely to the surface area which means that smaller the globule size, higher the surface area of the L-SNEDDS and hence higher the *in vitro* drug release. The results for *in-vitro* drug release are depicted in figure 3.2.

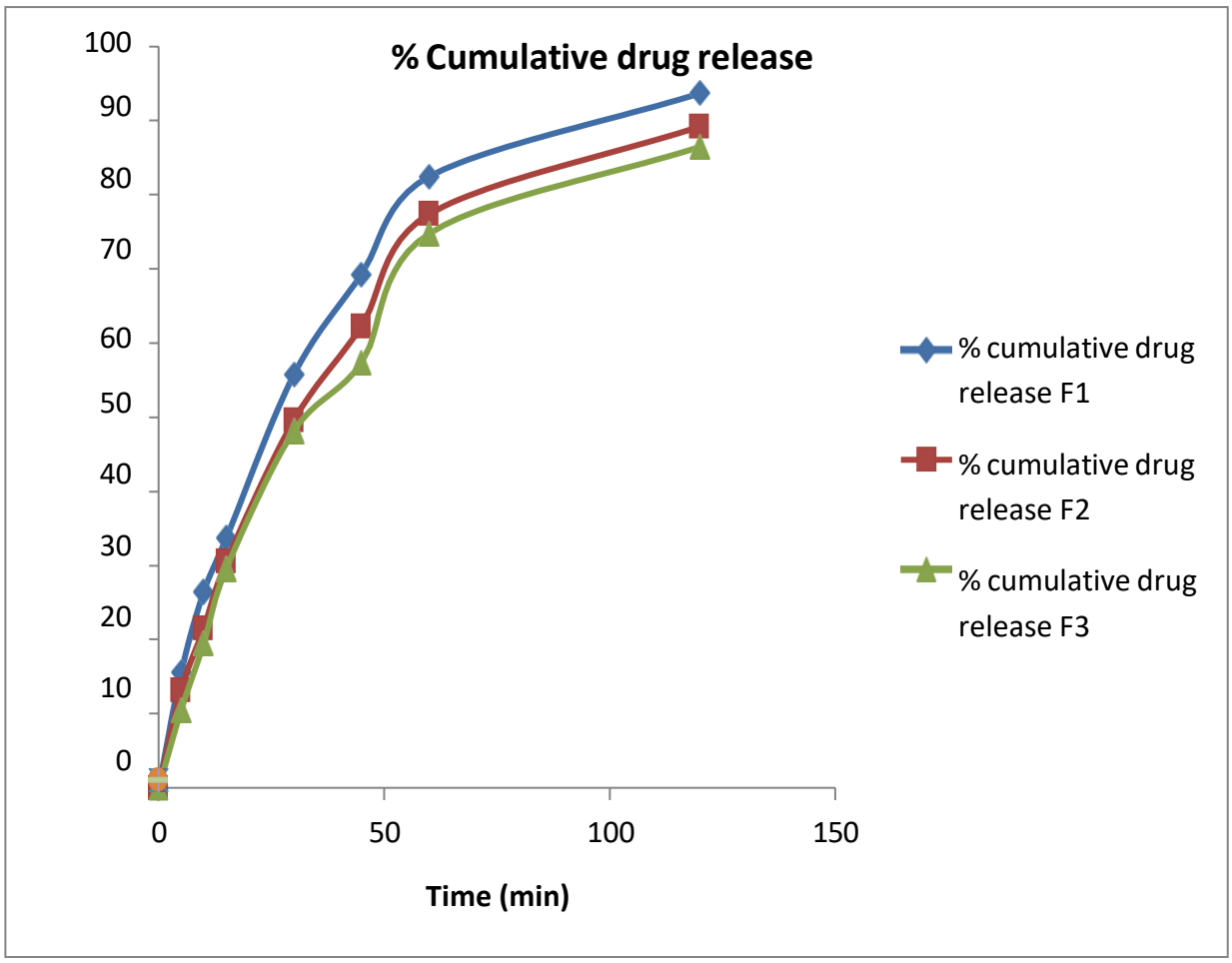

Figure 3.2 Graphical representation of % Cumulative drug release for L-SNEDDS (F1-F3)

3.2 Evaluation of S-SNEDDS

3.2.1 Micromeritic Properties of S-SNEDDS:-

The drug loaded S-SNEDDS were evaluated for Angle of repose, Bulk Density, Tapped Density, Carrs's Index and Hausner's Ratio and results are tabulated in table 3.2.

Table 3.2 Micromeritic Properties of S-SNEDDS (F1-F3) (mean ± S.D., n=3)

Formulation	Angle of repose	Bulk Density	Tapped Density	Carr's Index	Hausner's Ratio
F1	31.55 ± 0.27	0.584 ± 0.012	0.551 ± 0.021	12.27 ± 0.4	1.39 ± 0.002
F2	30.14 ± 0.24	0.475 ± 0.015	0.562 ± 0.017	13.83 ± 0.35	1.61 ± 0.005
F3	29.8 ± 0.3	0.441 ± 0.036	0.503 ± 0.019	12.36 ± 0.25	1.14 ± 0.003

3.2.2 Estimation of Drug Content

The drug content of S-SNEDDS was determined using a UV spectrophotometric technique that measured absorbance at 235 nm in phosphate buffer solution pH 7.4. The drug concentration was found to be between 96.84 and 98.2. The concentration of oil, surfactant, and co-surfactant had no effect on the drug content of the formulations. The results for all formulations are depicted in figure 3.3.

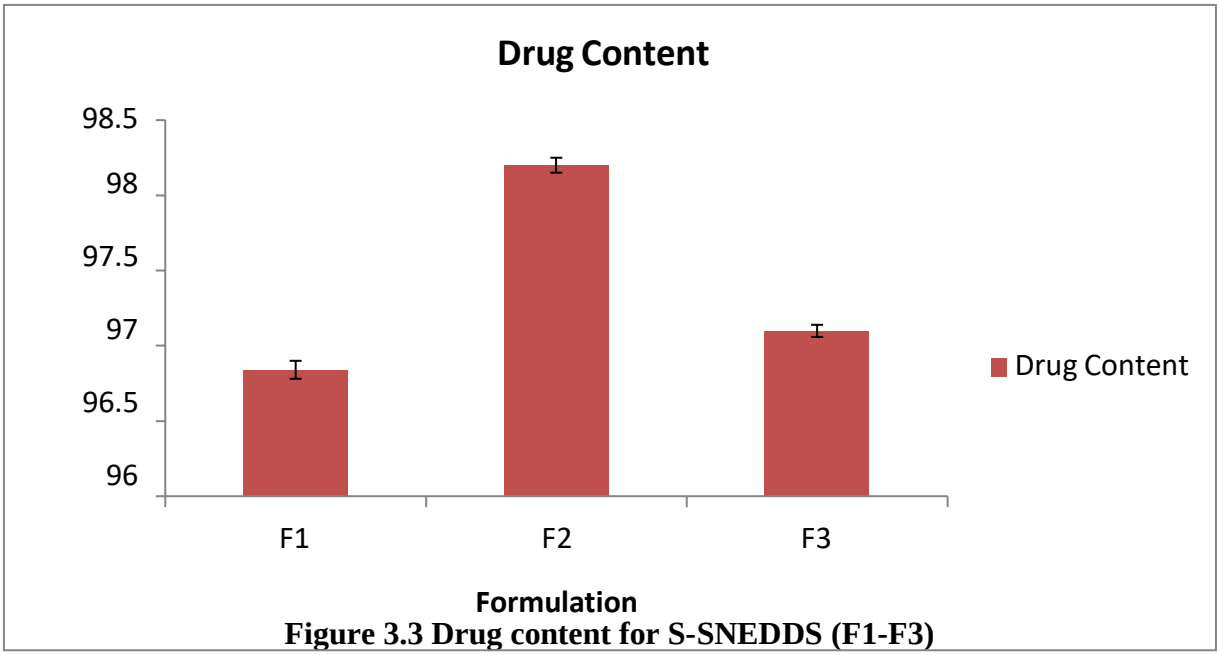

Figure 3.3 Drug content for S-SNEDDS (F1-F3)

3.2.3 Surface Morphology (SEM analysis)

The shape and surface morphology of S-SNEDDS were studied using Scanning Electron Microscopy (SEM). The S-SNEDDS were seen as smooth surfaced particles that agglomerated into large particles. It showed no crystalline shape that indicated that the L- SEDDS have complete adsorption on the surface of carrier used (Dextran 40). The photographs of S-SNEDDS are depicted in figure 3.4.

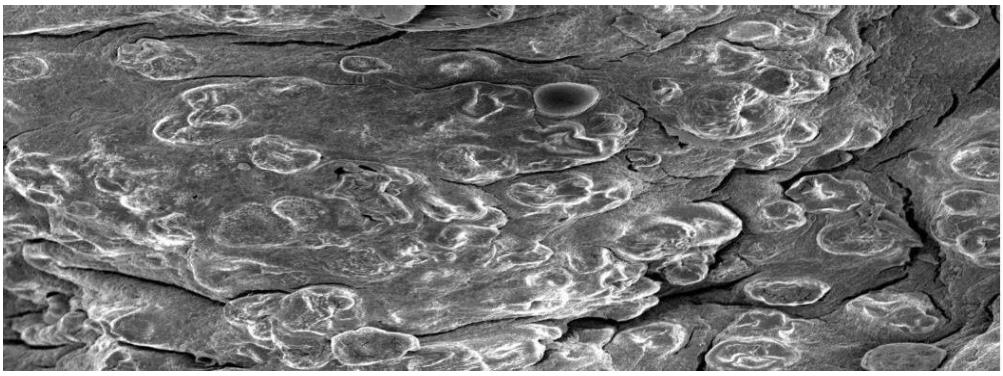

Figure 3.4 Scanning Electron micrograph of S-SNEDDS (F2)

3.2.4 *In vitro* Dissolution

The USP II dissolution test apparatus was used for the *in-vitro* drug release studies. The S- SNEDDS formulations showed drug release between 81.14 to 88.25% within 2hrs. The in vitro drug release data for S-SNEDDS followed a similar pattern to that of L-SNEDDS. However, there was only a little decrease in drug release, which can be due to the carrier (Dextran 40) used. The introduction of a carrier increases globule size, resulting in a decreased surface area and thus reduced in vitro drug release. The results for *in-vitro* drug release are depicted in figure 3.5.

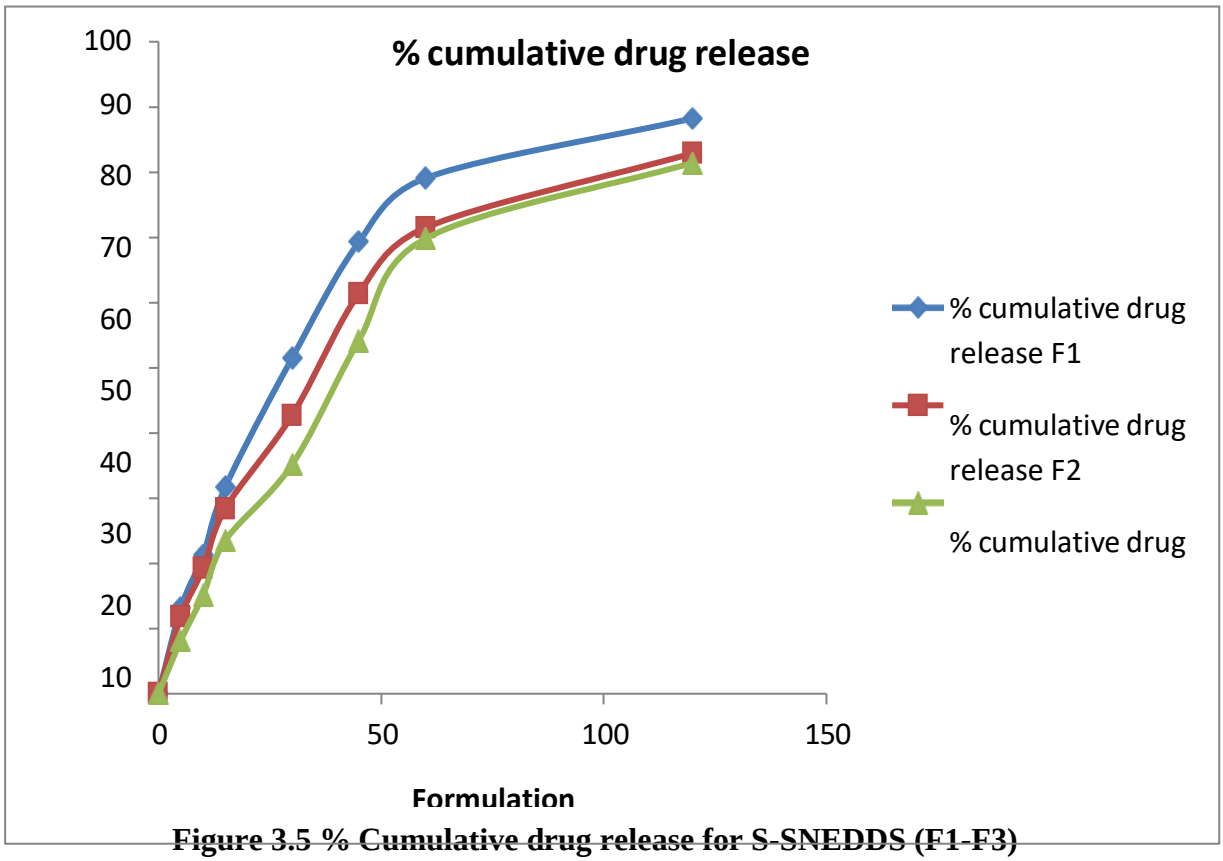

Figure 3.5 % Cumulative drug release for S-SNEDDS (F1-F3)

3.2.5 Stability Studies:-

The results from the stability studies indicated that S-SNEDDS remained unchanged even after 90 days of storage at varied temperature i.e., 25°C ± 2°C and 40°C ± 0.1°C. The formulations showed no phase separation and were transparent when seen visually. Even all formulations showed similar results on the aspects of drug content, *in vitro* drug release, phase separation. Hence, it was concluded that the formulations were stable at temperature extremities.

3.3 Determination of Release Kinetics:-

The mathematical models were used to evaluate the kinetics and mechanism of drug release. The model that gave high correlation coefficient (r) value was considered as the best fit of the release data. From the release kinetics of S-SNEDDS (Table 3.3), it was found that the Higuchi model was best fitted. The correlation coefficient (r^2) was used as an indicator of the best fitting and was found to be highest for Higuchi model kinetic(Figure3.6).

Table 5.13 Dissolution Characteristics of Drug loaded S-SNEDDS (F2)

Time (min)	5	10	15	30	45	60	120
Cumulative % drug released	11.8	19.2	28.4	42.7	61.4	71.5	82.9
% drug remaining	88.2	80.8	71.6	57.3	38.6	28.5	17.1
Square root time	2.236	3.162	3.872	5.47	6.7	7.74	10.95
Log cumulative % drug remaining	1.94	1.907	1.85	1.75	1.58	1.45	1.23
Log time	0.69	1	1.17	1.477	1.65	1.77	2.07
Log cumulative % drug released	1.071	1.28	1.45	1.63	1.788	1.85	1.91

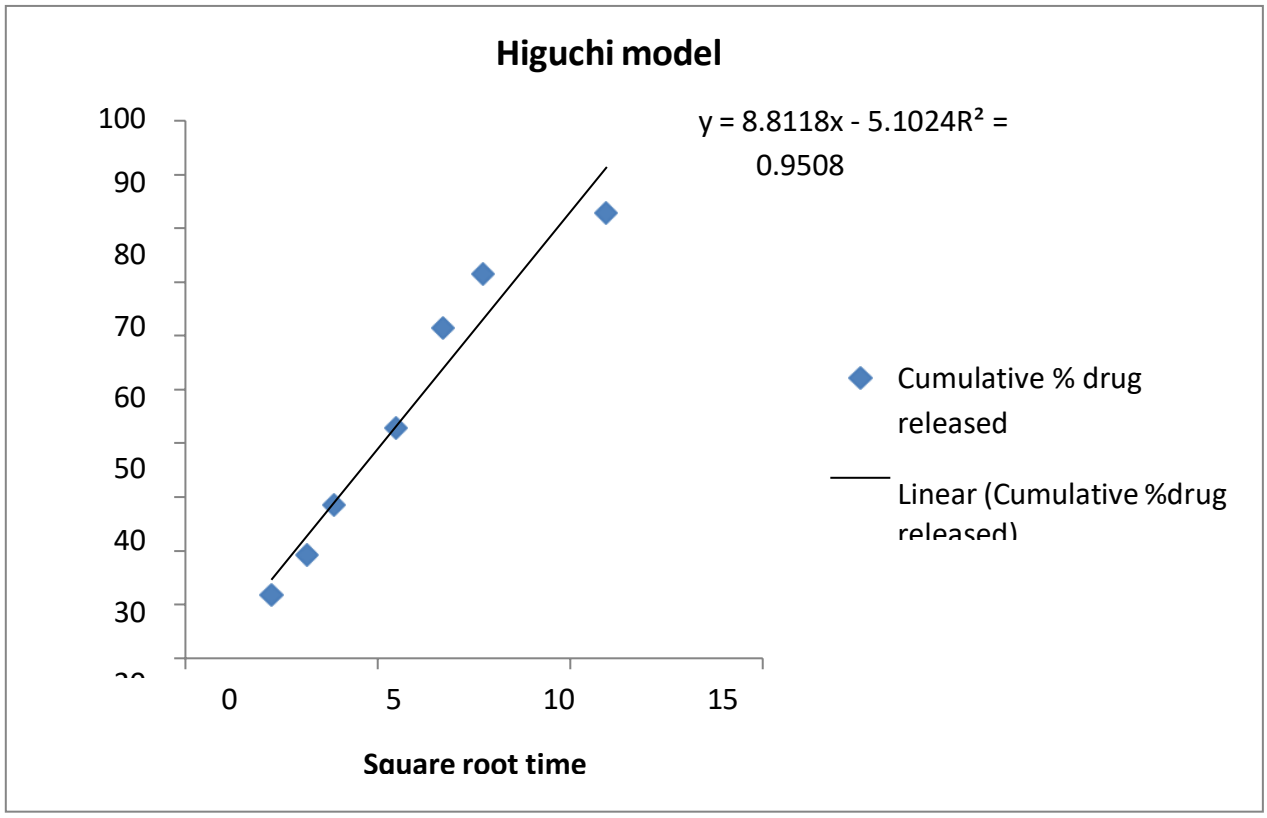

Figure 3.6 Higuchi model for S-SNEDDS

4. CONCLUSION:-

In this study, the SNEDDS were prepared by using different optimized oil phase (Ethyl oleate, olive oil and castor oil), surfactant (Tween 80) and co-surfactant (PEG 400). In the first step L-SNEDDS (F1-F3) were prepared and characterized on several parameters such as globule size, thermal stability, self emulsification, phase separation, pH, drug loading efficiency and in vitro drug release. The average globule size of L-SNEDDS was found to be in the nanoscale range.

All three formulations can be used on skin and will not cause any form of irritation or irritability and the drug loading efficiency increased with increase in oil concentration. The in vitro drug release pattern was found to be dependent on the globule size of L-SNEDDS. The characterized L-SNEDDS formulations were further used to prepare S-SNEDDS and were characterized on micromeritic properties, drug content, scanning electron microscopy and in vitro dissolution. The results from micromeritic studies indicated good flow properties and showed that the angle of repose increased with the increase in concentration of surfactant (Tween 80). The results from the in vitro drug release for S-SNEDDS also followed the similar pattern as with L-SNEDDS. But there was little drop in the drug release which can be attributed to the carrier (Dextran 40) used. The use of carrier increases the globule size which would ultimately leads to smaller surface area and hence reduced in vitro drug release. From the release kinetics of formulation F2 it was found that the Higuchi model was best fitted for S-SNEDDS. In a nutshell to

conclude, S-SNEDDS plays a vital tool in enhancing the therapeutic efficacy, improving the bioavailability, reducing the gastric irritation and sustaining the drug release.

5.ACKNOWLEDGEMENT:

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6. CONFLICT OF INTEREST:

None

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