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FORMULATION AND EVALUATION OF LAMOTRIGINE BASED SELF-NANO EMULSIFYING DRUG DELIVERY SYSTEM

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Abstract: Self-nanoemulsionof Lamotrigine (LMT), an anti-epileptic agent, having poor solubilty was formulated to improve the solubility and permeation. Co surfactant like Ethyl Oleate, Caprylate, Eucalyptus oil, Caprylic, Corn oil, Capmule, Fish oil, Coconut oil whereas PEG 400 and Propylene glycol to form the oil phase was selected as the oil. Seven trials were done using combination of sufactants/co-surfactants with oil phase . Trial H containing Caprylate as oil phase at S_{mix}1:1(Tween20/PEG400, 1:1) proportion and trial **I**, the oil phase [Caprylate] composition was changed from S_{mix} 1:1 to S_{mix} (Tween20/PEG400, 1:2) formulated as SNEDDs and phase diagram shows 1:1 system is suitable for formulation . Aqueous dilution test shows that it is found for 3 hour gradually turbid on staying. Since it immediately dissolve the drug as a result of solubilisation effect of surfactant present in formulation. Stability study was carried out at 25^{o} C/ 75 Rh. In this method no change in consistency, Colour or appearance has been observed. In vitro drug release was found to be identical in the formulations stored before after placed on stability. It appeared that the formulation of the selected batches kept on the stability test was found to be stable. In accelerated stability evaluation showed that Self nano-emulsion follows 1st order kinetic and found to be stable.

Keywords: Self nano-emulsifying drug delivery system, Lamotrigine, Nano-droplets, bioavailababability, lipophilic and co-surfactants.

Self-nano Emulsifying Drug Delivery System (SNEDDS):

Self-nanoemulsifying drug delivery systems (SNEDDS), spontaneously forming nano-droplets emulsion in water have acquired growing interest. SNEDDS are isotropic mixtures of drug, surfactant and co-surfactant that can rapidly form fine oil-in-water emulsions upon mild agitation in an aqueous media with a droplet size in the range 50-200 nm [*Lewena et al 1996 & Robinson et al*]. The dissolution of lipophilic drug in these nano-droplets combined with the small size and the larger surface area results in higher loading and improved bio availability of the drug [*Aungst et al 1993*].

Generally drug absorption occurs at the small intestine where absorption is more effective due to the presence of villi and microvilli [*Khoo et al 1998*]. To reach the intestine (pH 7.0-9.0) [*Charman et al 1992*], drugs must however resist the extremely low pH (pH 1.0-2.0) and enzymes in the stomach. Furthermore, some drugs could irritate the stomach, and, in addition, some lipophilic drugs have poor enteral absorption. Silibinin (also known as silybin), is a potent and principal component of silymarin extracted from the silybum marianum (Milk thistle) [*Groves et al 1974*]. Silibinin has been used as a natural remedy for hepatitis, cirrhosis and recently has been reported to possess anticancer activity [14]. Unfortunately, silibinin is poorly bioavailable, due to its degradation in the gastric fluid, low water solubility and poor enteral absorption [*Nazzal et al 2002*]. So far, there are no publications on self-

nanoemulsifying systems displaying pH sensitive properties. The aim of the present study was to develop a pH-sensitive self-nanoemulsifying drug delivery system (pH-SNEDDS) to increase solubility and dissolution of silibinin, thereby enhancing its oral bioavailability potentially. This formulation could moreover protect the drug from the acidic degradation in the stomach while facilitating the release in small intestine thanks to self-nanoemulsification. Drug solubility and loading in the formulations, nano-emulsions droplet size and stability, and *in-vitro* drug release have been evaluated.

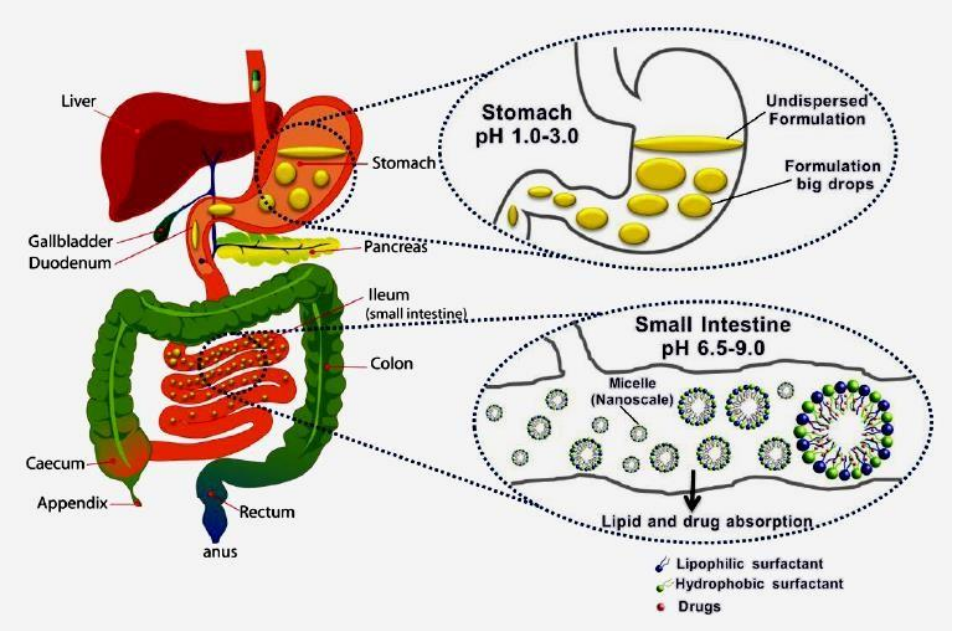


Figure 1-Schematic outline of the human digestive tract with pH-sensitive self-nanoemulsifying drug delivery system.*[Kawabata et al 2011]*

Advantage of SNEDDS

1. Increase oral bioavailability to allow for dosage decrease.
2. The deliberate administration of medications to a certain GIT absorption window.
3. Large drug loading.
4. Management of the delivery profiles.
5. Emulsions are metastable and sensitive dispersed forms, while SNEDDS are easily manufactured, physically stable formulations.
6. They provide a larger interfacial area for the medicine to be partitioned between oil and water as opposed to oily solutions.
7. By promoting and assisting in the medication's broad dispersion throughout the GI tract and stomach, SNEDDS helps to reduce the irritation that is sometimes experienced during prolonged contact between the bulk drug material and the gut wall.

Oral absorption of SNEDDS

SNEDDS partially avoids the additional drug dissolution step prior to absorption in the GI tract. They

increase the amount of solubilized drug in the intestinal fluids resulting in good drug absorption. Apart from this, absorption of the drug may also be enhanced by using lipid based excipients in the formulation. There are several mechanisms through which increased absorption can be achieved; the following schematic diagram describes these mechanisms.

Formulation components of SNEDDS:

- Drug
- Oil
- Surfactant
- Co-surfactant
- Co-solvent
- Consistency Builder
- Enzyme Inhibitors
- Adsorbents/solidifying agents
- Polymers

Selection of SNEDDS Components

1. **Oil:** The development of modified or hydrolyzed vegetable oils has been crucial to SNEDDSs' success owing to their formulation and physiological advantages. Oil can facilitate self-emulsification and increase the fraction of lipophilic drug transportation via the intestinal lymphatic system, thereby increasing absorption from the GI tract. [***Groves et al 1974***]
2. **Surfactant:** When SNEDDSs are made, non-ionic detergents are used. The usual surfactant concentration is between the ranges of 30–60% w/w of the formulation in order to form a stable SNEDDS. Surfactant having a high hydrophilic lipophilic balance (HLB) and hydrophilicity assists the immediate formation of o/w droplets and/or rapid spreading of the formulation in the aqueous media. Surfactants are amphiphilic in nature and they can dissolve or solubilize relatively high amounts of hydrophobic drug compounds. This can prevent precipitation of the

drug within the GI lumen. [***Wakerly at el 1986]*** Different surfactants (Cremophor EL, Cremophor RH 40, Solutol HS 15, Span 80, Tween 20 and Tween 80) were screened for emulsification ability of the selected oil phase. Surfactant selection was performed on the basis of %transparency and ease of emulsification. ***[Data et al 2007]***

3. **Co-surfactant:** Co-surfactant used in SEDDS helps to dissolve large amounts of hydrophilic surfactants or the hydrophobic drug in the lipid base, ***[Carli et al 2004].*** These solvents sometimes play the roll in 16 microemulsion systems. Six co-surfactants were screened for SNEDDS formulation, which included Carbitol, PEG 400, PG, Capmul MCM C8, Plurol oleique and Glycerol. The screening of the co-surfactants was conducted on the basis of % transparency and ease of emulsification. ***[Data et al 2007]***
4. **Drug:** Drug substance used in diagnosis, treatment or prevention of a disease or as a component of a medication used as a medicine which kills or inactivates germs that affects body function or origin.

MATERIALS & METHODS

Preformulation studies

Before we develop a dosage form, a prerequisite is to characterize the physico-chemical properties of the selected drug and excipients must be known. These data is vital for the subsequent stages in the formulation development. The objective of preformulation studies is to characterize the drug with known physiochemical properties, and generate a thorough understanding of the material's stability under the conditions that will lead to development of an optimal drug delivery system.

Drug and the exicipients which could be used in this study and its preformulation descriptions carried out by:

Organoleptic Parameters

Physical appearance: White

Nature: Crystalline powder

Odor: None

Melting point: 220^{o}C

Identification of Drug & Excipients

FTIR spectroscopy

FT Infra-red absorption spectrum of drug and excipients (I.R.) were characterized using Shimadzu. FT-IR spectrophotometer using standard Potassium bromide pellet method. Powder sample approx 5mg and KBr 200mg were taken in mortar and grounded using the pestle. Transfer the powder into the KBr pellet press and allow hydrolylauic force to be applied to get KBr pellet. Place the pellet into the sample holder of the IR instrumentation and record the FTIR data in the range of 400-4000cm^{-1} range.

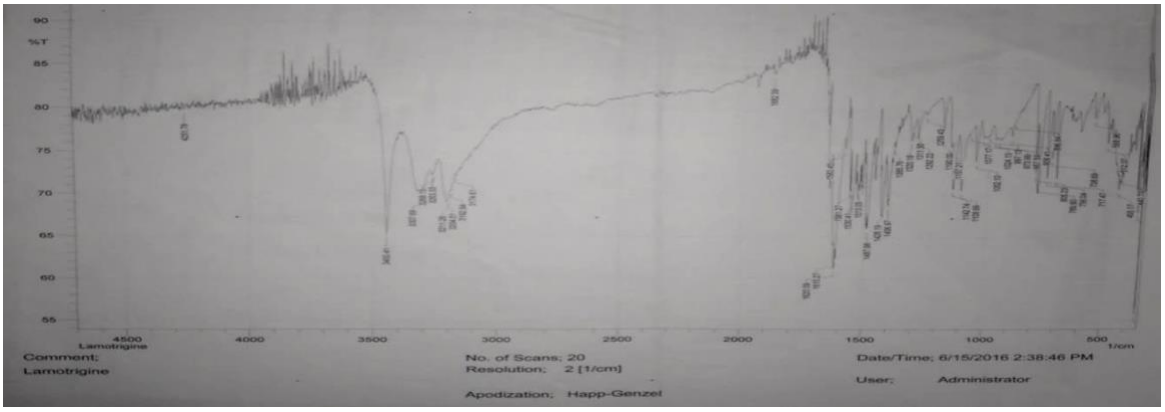


Figure 2: **FTIR Spectra of Lamotrigine**

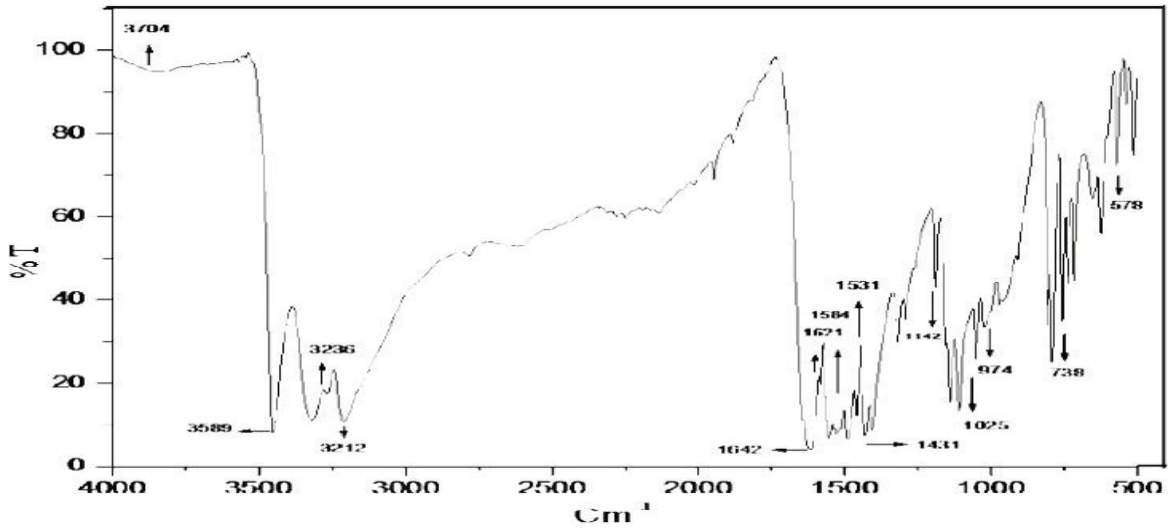
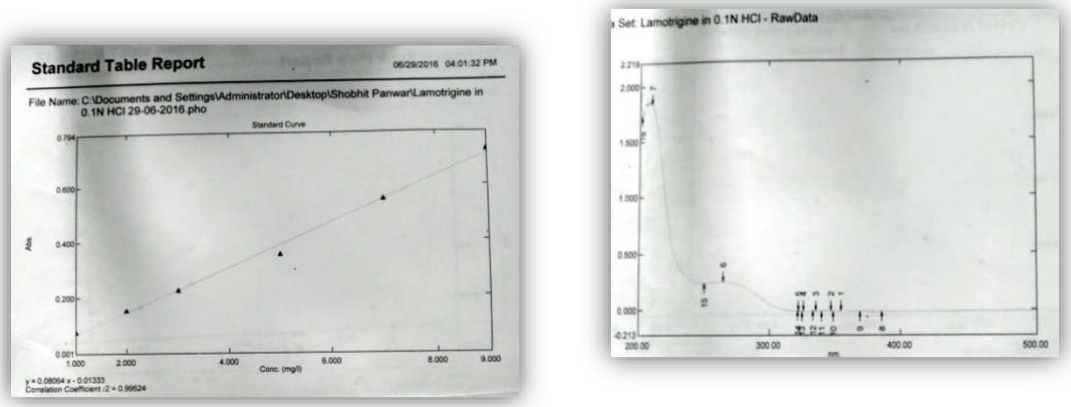


Figure 3: FTIR spectra of Lamotrigine reference [*Ramya et al 2014*]

UV Spectrophotometry

UV spectrum of procured sample was taken using U.V-Visible spectrophotometer (SCHIMADZU, UV-1700). Sample (10.0mg) was weighed and transferred to 10 ml into each volumetric flask and diluted with [a] 0.1N HCl [b] Ethanol [c] Citric acid buffer(4.5 pH) prepare stock solution. It was diluted to 100 times and its UV spectrum was determined as given in fig.2.5-2.12 UV spectrum of

the procured sample of Lamotrigine showed one absorption maxima at max 265.0 nm which is identical with reported value in Indian Pharmacopoeia 1996.



[a] [**b**]

Figure 4 – UV Standard curve of Lamotrigine in Hydrogen chloride 0.1 N [a] and its UV spectrum [b]

Table 1: Standard curve of Lamotrigine in 0.1N HCl determined at max 265nm

Concentration [mcg]	**Mean absorbance ± SD**
1.0	0.078±0.005
2.0	0.155±0.003
3.0	0.227±0.001
5.0	0.357±0.003
7.0	0.552±0.002
9.0	0.728±0.004

Table 2: Spectrophotometric estimation of drug in different solvent systems and its parameters

Solvent system	λ_{max} value	Range	Equation of line ($y=mx+c$)	Correlation coefficient (r^2)	Stability
0.1N HCl	265	1-9	Y=0.080x-0.0133	0.995	Stable
Ethanol	306	1-9	y=0.081x+0.098	0.956	Stable

Citric acid buffer	267	1-9	y=0.083x+0.039	0.986	Stable

Prepared at temperature =25 ±1°C,

Solubility study of Lamotrigine in different excipients

Drug solubility was measured in different excipients (surfactant, oil phase and co-solvents). It was determined by dissolving excess amount of Lamotrigine to be taken in vials containing 0.50 ml of excipient and allowed to be kept till the drug become saturated in solvent.

Each vial was kept agitated for 48 hours in wrist shaker at constant temperature. Vials were removed and centrifuged at 3000rpm for 10 minutes. Undissolved drug was removed and filtered off with Whattman filter paper. The quantity of drug dissolved was determined by spectrophotometer method using the following formula.

Solubility (μg/ml) = (Absorbance × dilution factor)/slope)

Oil

1. Corn oil
2. Fish oil
3. Coconut oil
4. Capmule
5. Ethyle oleate
6. Eucalyptus oil
7. Caprylate

Surfactant

1. Tween 20
2. Tween 80

Co-surfactant

1. PEG400

Stabilizer

1. Egg lecithine

Table 3: Solubility of Lamotrigine in Excipients

	No Co Surfactant		**With PEG400**	
	Tween20	Tween80	Tween 20	Tween80

Corn oil	Slight Mis	Slight Mis	Slight Mis	Slight Mis
Eucalyptus oil	Slight Mis	Slight Mis	Mis	Mis
Fish oil	Slight Mis	Slight Mis	Mis	Mis
Coconut oil	Slight Mis	Slight Mis	Slight Mis	Slight Mis
Capmule	Slight Mis	Slight Mis	Mis	Mis
Ethyle olate	Slight Mis	Slight Mis	Mis	Mis
Caprylate	Slight Mis	Slight Mis	Mis	Mis

DRUG EXCIPIENT COMPATIBILITIES

Drug-excipient compatability were studied using FTIR Spectroscopy.

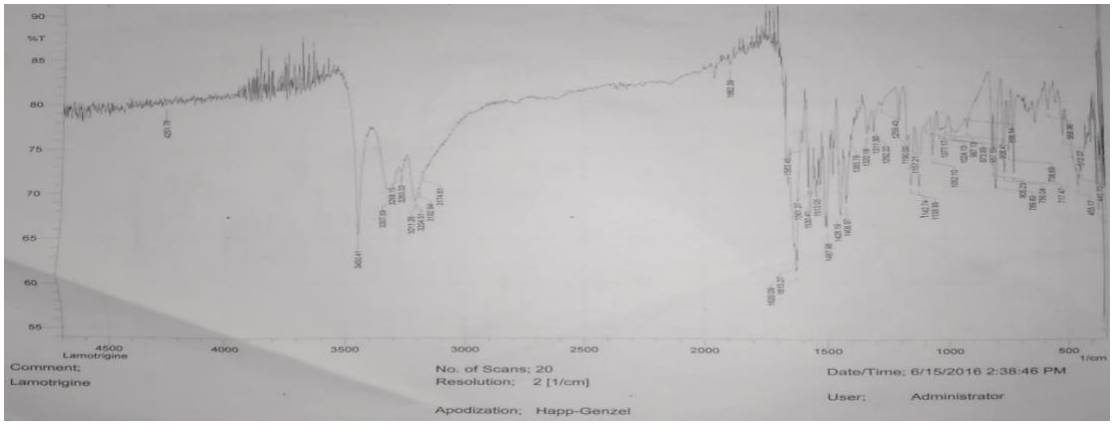


Figure 5 – FTIR Spectra of sample Lamotrigine.

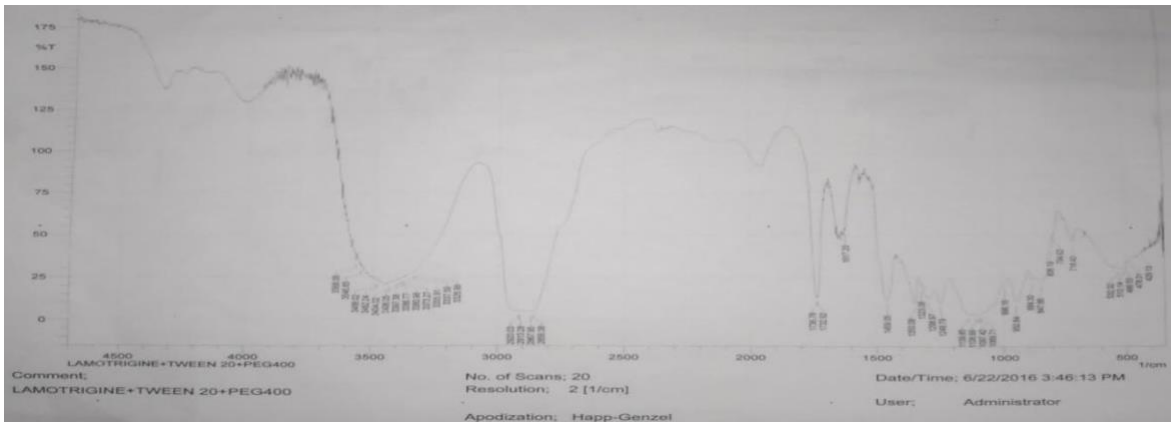


Figure 6– FTIR spectra of sample Lamotrigine with Tween 20 and PEG400

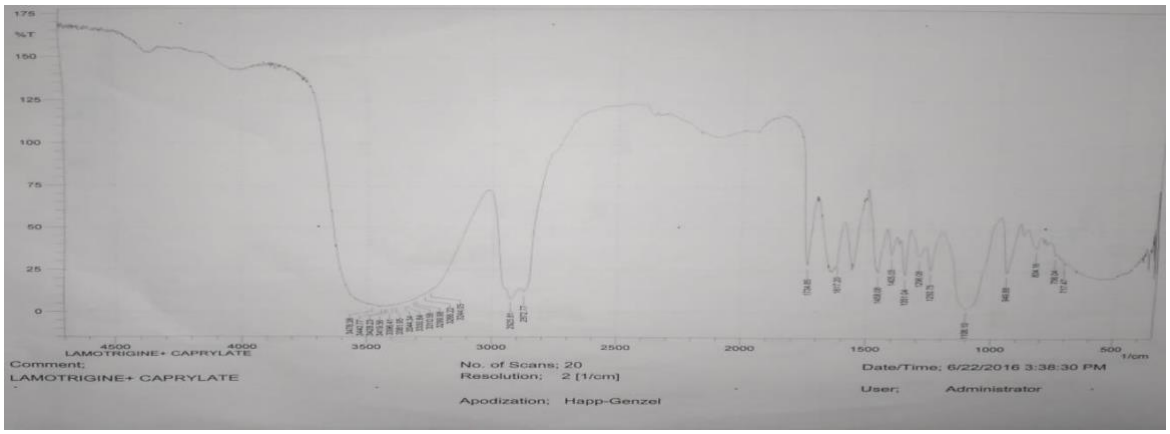


Figure 7– FTIR Spectra with Caprylate, Tween 20 and PEG 400

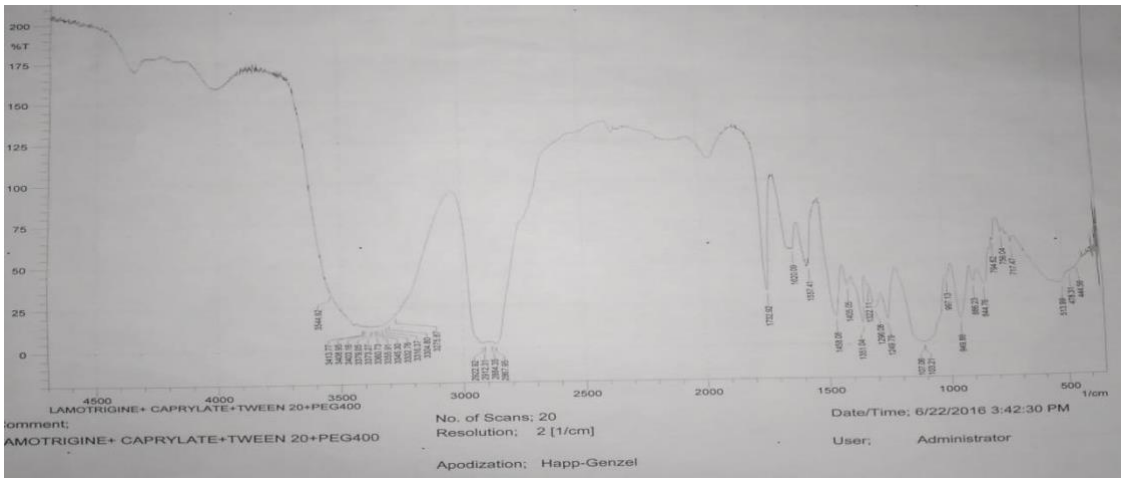


Figure 8– FTIR Spectra of Lamotrigine and Caprylate

Aqueous Dispersibility of Trial batches (Pre-concentrate mix)

For the preparation of SNEDDS, firstly we work on a system which is produced by the various components like oil, surfactant, co-surfactant which is self-emulsified and gives us the stable and clear formulation after the addition of water. The resulted transparent system further diluted and examined in excess of water. After visual inspection, the quantity of water required to make the preconcentrate remained in transparent form was determined.

Trial batches of preconcentrate mix to screen out the possible components required to make dilutable SNEDDS.

Trial

1. Take 10ml beaker and weight tween20 & PEG400 in variable ratio quantity. It is called as

surfactant/co-surfactant mixture.

2. Take 100mg of corn oil in another beaker of 10ml capacity and transfer the mixture of surfactant/co-surfactant.

3. Add the quantity of water to above beaker contain oil and Smix.

4. Initially add quantity of water and shake well till clear solution is observed.

5. Further addition of water should be made till the clear system is last.

6. Determine the quantity of water needed to lose the clarity of solution.

Table 4 - Trial [A] composition prepared using S_{mix} (1:1) withCorn oil.

TRIAL NO	CORN OIL[mg]	TWEEN 20 [mg]	PEG400 [mg]	WATER [mg]	VISUALLY EXAM. [mg]
A1	100	150	150	400	Turbid
A2	100	250	250	400	Turbid
A3	100	350	350	400	Turbid
A4	100	550	550	400	Turbid
A5	100	750	750	400	Turbid

For the trial no A1, 100mg corn oil was selected, after that tween20 and PEG400 was taken in different ratio, each mg and added to the oil and after proper mixing water was added but the result was not clear and that give a turbid system. That means the system can't be selected foe SNEDDS.

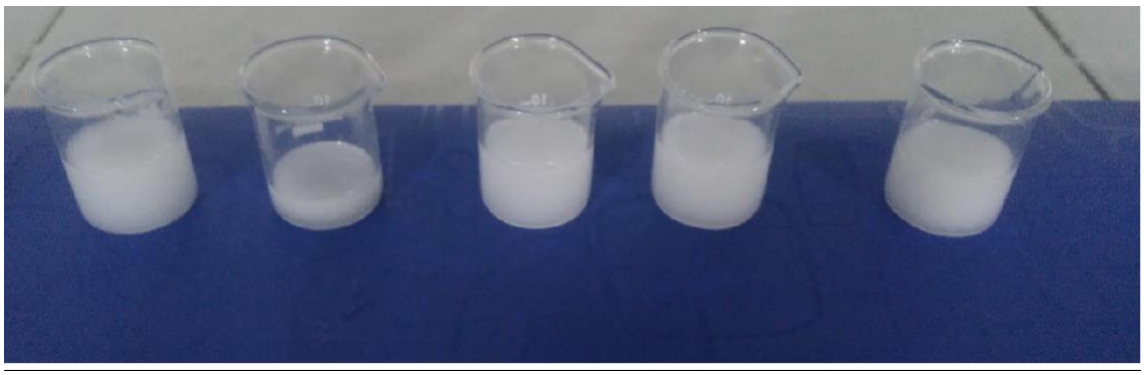


Figure 2.8- Trial [A] Composition prepared using S_{mix} (1:1) withCorn oil.

Table 5- Trial [B] composition prepared using Fish oil.

Trial No	Fish Oil [mg]	Tween 20 [mg]	Peg400 [mg]	Water [mg]	Visually Exam. [mg]
B1	100	250	250	100	Turbid

B2	100	300	300	130	Turbid
B3	100	500	500	150	Turbid
B4	100	750	450	130	Turbid
B5	100	800	400	150	Turbid

For the trial of fish oil, quantity of fish was taken 100 mg tween20 and PEG400 was selected as surfactant and co-surfactant, random quantity of tween and PEG was taken but the result shows the turbid system at the end. Consistently quantity of T/PEG increased but result was again unsuccessful when water was added, and resulted turbid system.

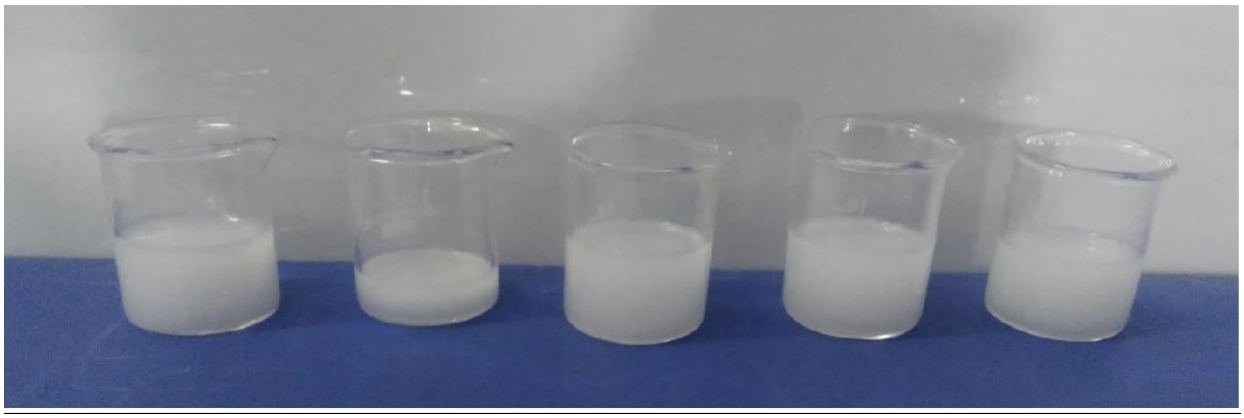


Figure 9- Trial [B] Composition prepared using Fish oil.

Table 6- Trial [C] composition prepared using Coconut oil.

TRIAL NO	Coconut OIL [mg]	TWEEN 20 [mg	PEG400 [mg]	WATER [mg]	VISUALLY EXAM. [mg]
C1	100	400	400	100	Turbid
C2	100	600	600	150	Turbid
C3	100	800	800	200	Turbid
C4	100	1000	500	100	Turbid
C5	100	1200	600	200	Turbid

For the third trial of SNEDDS system preparation we worked on Coconut oil as the primary phase. Tween20 and PEG400 were mixed in to the 100mg quantity of oil as the ratio in table but as result we can see that it shows the rapid turbidity when very less water added into that.

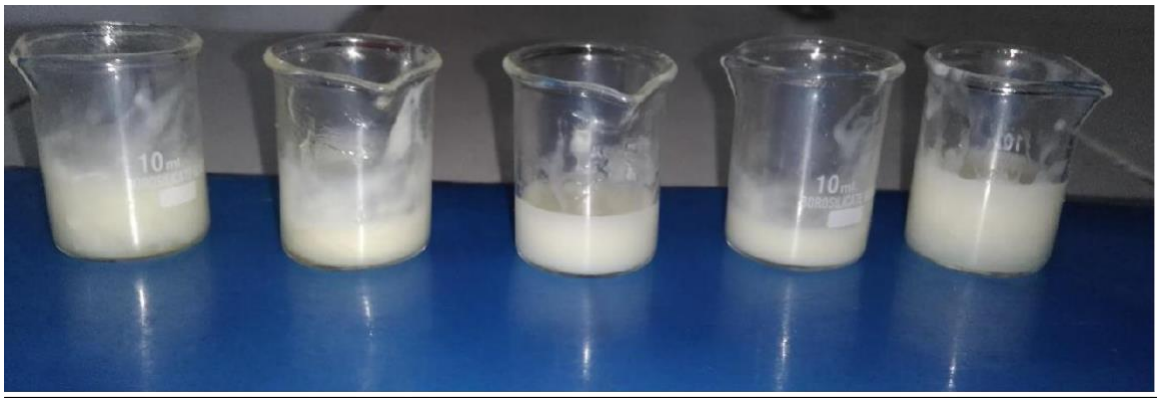


Figure 10- Trial [C] Composition prepared using Coconut oil.

Table 7- Trial [D] Composition prepared by using S_{mix} 1:1 with Ethyl Oleate and Lecithine.

TRIAL NO	ETHYL OLEATE[mg]	LECITHIN	TWEEN 20 [mg	PEG400 [mg]	WATER [mg]	VISUALLY EXAM. [mg]
D1	100	5	200	200	100	Clear
D2	100	5	300	300	120	Turbid
D3	100	5	600	600	150	Turbid
D4	100	5	750	750	180	Turbid
D5	100	5	800	800	200	Turbid

We added lecithin 5% in ethyl oleate to improve the stability of SNEDDS but the problem remains the same and in addition of water in S_{mix} it resulted the turbid system.

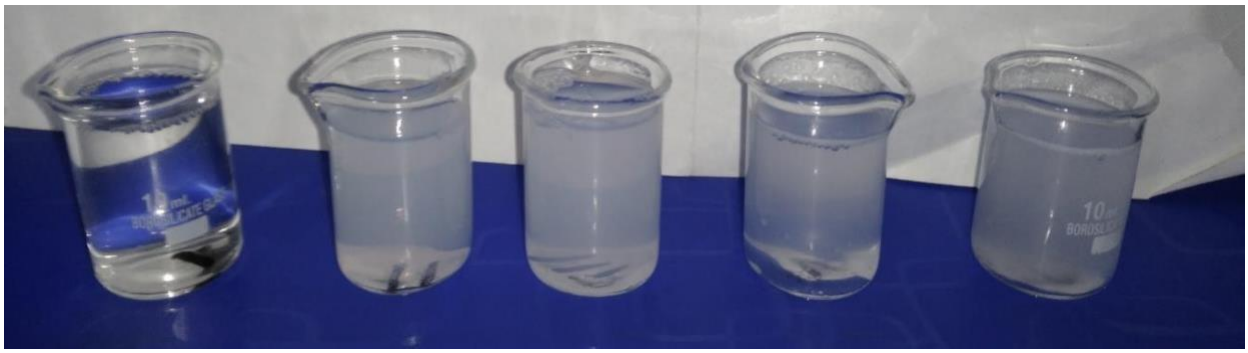


Figure 11- Trial [D] Composition prepared by using S_{mix} 1:1 with Ethyl Oleate and Lecithine.

Table 2.8- Trial [E] Composition prepared using S_{mix} in Different Ratio with Ethyle Olate

Trial	S_{mix}	Ratio	oil	Water	Visual examination

E1	Tween20/PEG400	1:1	Ethyloleate	120	Turbid
E2	Tween20/PEG400	1:2	Ethyl oleate	120	Turbid
E3	Tween20/PEG400	1:3	Ethyl oleate	120	Turbid
E4	Tween20/PEG400	2:1	Ethyl oleate	200	Turbid
E5	Tween20/PEG400	3:1	Ethyl oleate	200	Turbid

Figure12- Trial [E] Composition prepared using S_{mix} in Different Ratio with Ethyle Olate

Table 8- Trial [F] Composition prepared using Smix(1:1) with Capmule

Trial	Tween20/PEG400	Capmul(mg)	Water(mg)	Visually examination
F1	600	50	650	Clear
F2	600	75	650	Clear
F3	600	100	650	Clear
F4	600	150	650	Clear
F5	600	200	650	Turbid

Table 9- Trial [G] Composition prepared using Smix(1:1) with Eucalyptus oil

Trial	Tween20/PEG400	Eucalyptus oil	Water(mg)	Visually examination

G1	300	50	500	Clear
G2	300	75	500	Clear
G3	300	100	500	Clear
G4	300	150	500	Clear
G5	300	200	500	Turbid

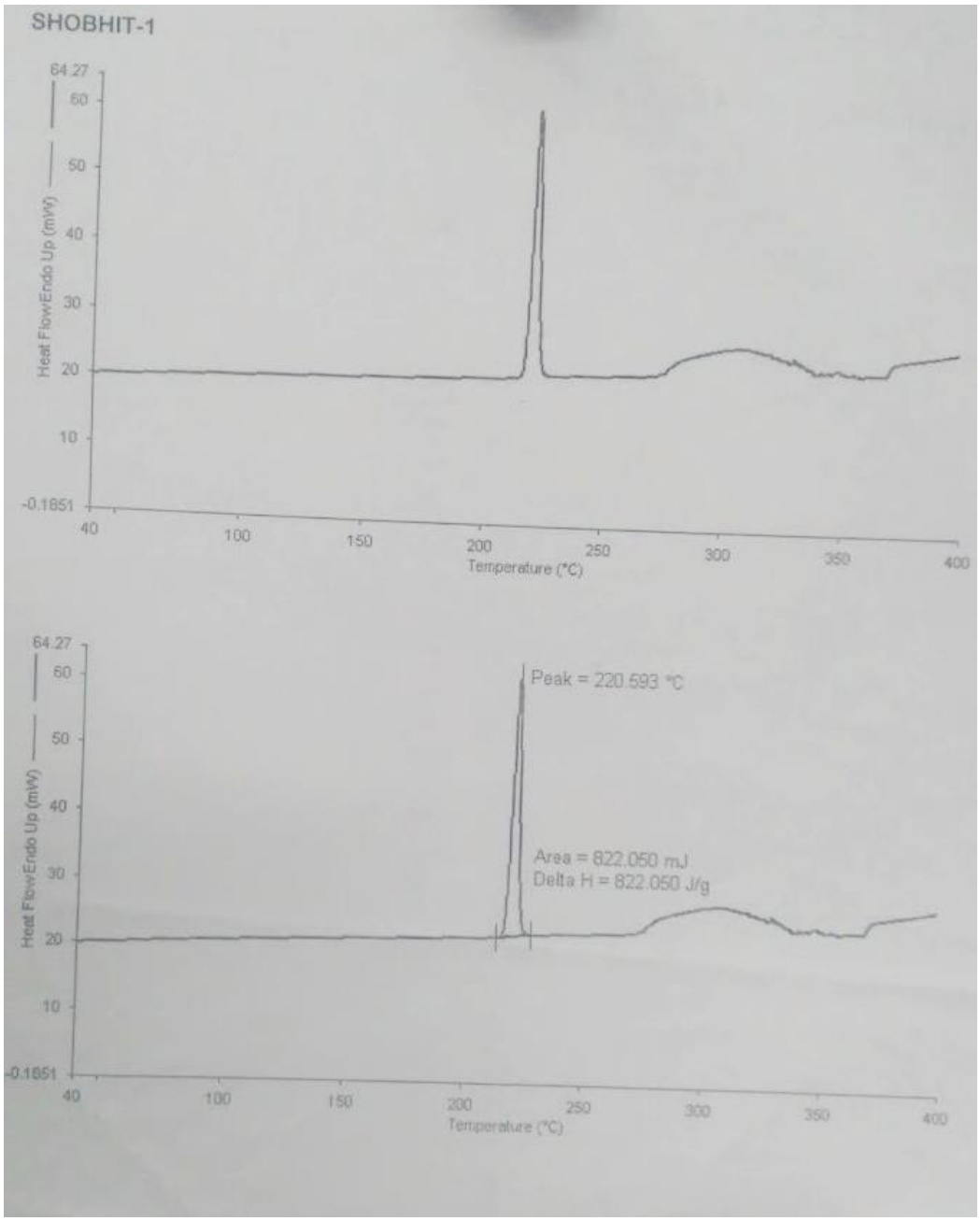
Table 10- Trial [H] Composition prepared using S_{mix} (1:1) with Caprylate

Trial	Oil	S_{mix}1:1 Tween20/PEG400	Water	Visual examination
H1	100	300	100	Clear
H2	100	300	500	Clear
H3	100	300	800	Clear
H4	100	300	1000	Clear
H5	100	200	200	Clear
H6	100	200	500	Clear
H7	100	200	1000	Clear
H8	100	100	200	Clear
H9	100	100	400	Clear
H10	100	100	800	Clear
H11	200	100	400	Clear
H12	200	100	800	Clear
H13	200	100	1200	Clear
H14	200	100	1000	Clear
H15	300	100	500	Clear
H16	300	100	1000	Clear
H17	300	100	1500	Clear
H18	400	100	500	Clear
H19	400	100	1000	Clear
H22	400	100	15000	Bluish
H23	500	100	800	Clear
H24	500	100	1200	Clear
H25	500	100	1800	Clear
H28	500	100	6000	Turbid

Table 11- Trial [I] Composition prepared using S_{mix}(1:2) Caprylate

Trial	Oil	S_{mix}1:2 Tween20/PEG400	Water	Visual examination
1	100	300	300	Clear
2	100	300	500	Clear
3	100	300	700	Clear
4	100	300	100	Clear
5	100	200	300	Clear
6	100	200	600	Clear
7	100	200	900	Clear
8	100	100	300	Clear
9	100	100	500	Clear
10	100	100	1000	Clear
11	200	100	200	Clear
12	200	100	300	Clear
13	200	100	600	Clear
14	200	100	1000	Clear
15	300	100	500	Clear
16	300	100	1000	Clear
17	300	100	1500	Clear
18	400	100	500	Clear
19	400	100	1000	Clear
20	400	100	2000	Clear
21	400	100	3000	Clear
22	400	100	6000	Bluish
23	500	100	1000	Clear
24	500	100	2000	Clear
25	500	100	3000	Clear
27	500	100	4000	Clear
28	500	100	5000	Turbid

Figure 13 – Trial [I] Composition prepared using S_{mix}(1:2) Caprylate



CONCLUSION:

In this study, SNEDDS was formulated and further developed using lamotrigine as carrier drug with co-surfactants and oil phase. From this study, it was concluded that the prepared formulated was thermodynamically stable with good self-emulsification efficiency and having globule size in the range of 267 nm which may bephysiologically stable. It was also concluded thatSNEDDS follows first order kinetics. Self-emulsifying drug delivery systems represented a prominent approach improving problems like bioavailabilty and aqueous solubility and stability parameters.

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