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FORMULATION AND EVALUATION OF SOLID-SELF NANO EMULSIFYING DRUG DELIVERY SYSTEM OF FAMOTIDINE

D. Prasanthi *, G. Meghana and V. Navya

G. Pulla Reddy College of Pharmacy, Mehdipatnam, Hyderabad - 500028, Telangana, India.

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Correspondence to Author:
Dr. D. Prasanthi

Associate Professor,
G. Pulla Reddy College of Pharmacy, Mehdipatnam, Hyderabad - 500028, Telangana, India.

E-mail: prasanthidhanu@gmail.com

ABSTRACT: The main objective of the study was to formulate and evaluate solid self nano emulsifying drug delivery systems (SNEDDS) of famotidine (BCS class-IV drug), a histamine receptor antagonist used in case of ulcers, Zollinger-ellison syndrome. Liquid SNEDDS was formulated using oils like oleic acid, arachis oil, surfactants like Tween 20, Tween 80, etc., and co-surfactants like Transcutol-P, polyethylene glycol. Based on solubility studies, oleic acid (15mg/ml), Tween 20 (38.41mg/ml) & Transcutol-P (2.593mg/ml) were further studied by phase titration method using different ratios of oil: s-mix (surfactant: co-surfactant) from 1:9 to 9:1 with pseudo-ternary phase diagrams. FTIR spectra indicated drug excipient compatibility. Further evaluation studies, namely thermodynamic stability studies, robustness to dilution, self-emulsification time, dispersibility test, drug content, and *in-vitro* drug dissolution tests, formed the basis for optimization of liquid SNEDDS formulation. *In-vitro* drug release of F1 (97.15±0.02% in 90 min) and F19 (100.23±0.1% in 60 min) was significantly higher when compared to the pure drug (18.41±0.01% in 90 min). The droplet size of F19 (ratio of 3 (oil): 1 (s-mix), smix ratio (2:8)) was found to be 102nm, PdI 0.365 and zeta potential of -12.2mV. Formulations F1 & F19 were converted to Solid-SNEDDS by adsorption onto Neusilin US2 carrier. The Solid F19 capsule formulation has shown *ex-vivo* permeation of (96.98±0.1%) when compared to the pure drug (44±0.08%) in 120 min. XRD and DSC studies confirmed the conversion of the crystalline drug to its amorphous form. The surface morphology of solid F19 was studied. Hence, solid-SNEDDS enhanced the solubility and permeation of the drug.

INTRODUCTION: Self nanoemulsifying drug delivery systems (SNEDDS) are isotropic homogenous mixtures of an active compound in a combination of natural or synthetic lipids, surfactants, and co-solvents [1]. These anhydrous liquid mixtures are commonly termed as pre-concentrates.

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Upon gentle agitation in an aqueous phase, such as the upper GI lumen content, these pre-concentrates spontaneously form drug-encapsulated O/W micro/nano-emulsions with a particle diameter of 200 nm or less, contrary to emulsions and suspensions. The O/W emulsion distributes throughout the GIT and absorption of lipid, and the drug occurs in the small intestine [2].

Self-emulsifying drug delivery systems (SEDDS) are highly thermodynamically stable formulations, as they comprise of surfactant and co-surfactants mixture. SNEDDS are converted into solid dosage forms like tablets or either filled into soft/hard gelatin capsules or hydroxypropylmethylcellulose

capsules, which makes them commercially viable and more patient compliant [3]. Drugs belonging to BCS class II (low solubility, high permeability) and class IV (low solubility and permeability) display poor bioavailability, which can be formulated as SNEDDS to enhance bioavailability for oral route of administration [4].

SNEDDS offer advantages compared with ready-to-use nanoemulsions; bioavailability can be enhanced using a self nanoemulsifying drug delivery system. Large quantities of the lipophilic drug can be dissolved in SNEDDS and can also prevent the drug from enzymatic action making them suitable for parenteral route [5]. SNEDDS are advantageous over SEDDS as the former are less dependent on bile salts for the formation of droplets, by which better absorption of the drug is expected compared to SEDDS. SNEDDS possess higher physical and/or chemical stability even upon long-term storage because of the low energy consumption. SNEDDS can be formulated as liquids, sprays, ointments, creams, foams, and gels [6]. It can also be used in several drug delivery systems such as topical, oral and parenteral nutrition [7].

Drugs that cause irritation in GIT on prolonged contact can be formulated as SNEDDS as they disperse as fine droplets, which can widely distribute throughout the GIT and transported from the stomach[8]. Patient compliance and palatability can be improved as SNEDDS can be filled into soft/hard gelatin capsules [8]. The disadvantages of SNEDDS are a higher concentration of surfactant, and their chemical stability can lead to gastric irritation. SNEDDS are not very suitable for controlled drug release. Migration of volatile co-solvents in hard gelatin capsules may lead to hardening of the shell and precipitation of the lipophilic drug [9]. The L-SNEDDS are converted into S-SNEDDS using different solidification techniques. Capsule filling is the simplest technology for the encapsulation of liquid or semisolid formulations for the oral route. Capsule filling is advantageous due to its simplicity of manufacturing, high drug loading potential and suitability for low-dose, highly potent drugs [10]. In the spray drying technique, the solubilized liquid formulation is then atomized into a spray of droplets. The droplets are then dried, where the volatile phase evaporates, forming dry particles under controlled temperature and airflow conditions. In the melt granulation technique, powder agglomeration is obtained through the addition of a binder that melts or softens at relatively low temperatures. Melt granulation is advantageous over conventional wet granulation as there is no requirement for liquid addition and drying [4]. L-SNEDDS can also be converted into free-flowing powders by adsorption to solid carriers. It is a simple process and involves the addition of L-SNEDDS onto the solid by mixing in a blender. This free-flowing powder can either be filled into capsules or can be mixed with suitable excipients and compressed into tablets. The free-flowing powders possess a large surface area and an ability to adsorb around 70% W/W of their own weight [5, 6]. A significant advantage of the adsorption technique is content uniformity.

A phase diagram is constructed to capture the relationship between the phase behaviour of a mixture and its composition. Pseudo ternary phase diagrams aid in characterizing the zone of micro-emulsion. Each of the three corners of the phase diagram represents 100% of that particular component. Pseudo ternary phase diagrams were constructed using a predetermined amount of oil, surfactant, co-surfactant. The mixtures of surfactant: co-surfactant was formulated in different ratios (1:1, 1:2, 1:3). The ratio of oil: Smix (surfactant:co-surfactant) was also varied from 9:1 to 1:9. Water was added drop by drop to a predetermined amount of oily mixture under constant magnetic stirring, and the samples were observed visually after 24 hrs. Cut and weight system was used to determine the total area of phase diagram occupied by each system. The main objective of the present research work is to develop solid self-nano emulsifying drug delivery systems of the poorly water-soluble drug, famotidine, a histamine H2 blocker with antacid activity mainly used in case of ulcers, GERD, zollinger-ellision syndrome. It is a BCS class IV drug *i.e.*, poorly soluble and poorly permeable.

MATERIALS AND METHODS:

Materials: Famotidine was a gift sample from Suven life sciences. Oleic acid (cis-9-octadecenoic acid, (Z)-octadec-9-enoic acid) was bought from Molychem.

Tween 20 (polysorbate 20 monooleate), Tween 80 (polysorbate 80 sorbitan monooleate) were bought from Sisco research laboratories pvt. Ltd. Transcutol P (Diethylene glycol monoethyl ether) was bought from Alfa Aesar – A Johnson Matthey company. Neusilin US2 (Amorphous Magnesium Aluminometasillicate), Prosolv SMCC 50 (silicate microcrystalline cellulose), and Fujicalin (Dibasic calcium phosphate anhydrous) was obtained as a gift sample from Gangwal Chemicals Pvt. Ltd.

Method of Preparation: The L-SNEDDS were prepared by the phase titration method. The drug was added to the co-surfactant, and at 60°C, oil was added drop by drop with continuous stirring. As the drug gets solubilized, the formulation was brought back to room temperature and the surfactant was added slowly dropwise with gradual stirring. This mixture is known as the self-nano emulsifying drug delivery system. Water is then added dropwise to the total content for diluting the sample with continuous stirring.

Solubility Studies: This study involves the identification of various oils, surfactants, and co-surfactants in which famotidine shows maximum solubilizing ability. The method involves addition of drugs in excess to 2ml solvent, which are filled in vials. The vials were shaken for 48-72 hours in an orbital shaker to achieve homogenous slurry. The samples were then subjected to centrifugation at 4500 rpm for 10 minutes to obtain a supernatant followed by filtration of aliquots of supernatant using a syringe filter. The filtrate obtained was diluted with water, analyzed at 276 nm by UV spectrophotometer for quantification of the drug content [10]. The solubility studies form the basis of selection for oil, surfactant, and co-surfactant.

Construction of Pseudo-ternary Phase Diagram: Pseudo ternary phase diagrams were constructed to examine the formation of oil in water emulsions using four components, namely oil, surfactant, co-surfactant, and aqueous system. Based on the solubility study, the oil, surfactant and co-surfactant were selected. Surfactant and co-surfactant (Smix) in different weight ratios (1:1, 1:2, 1:3, 1:4, 2:1, 3:1, 4:1) were mixed in each group. These Smix ratios were chosen in increasing concentration of surfactant with respect to co-surfactant and increasing concentration of co-surfactant with respect to surfactant for extensive study of the phase diagrams. For each phase diagram, drug, oil and surfactant/co-surfactant mixture was mixed thoroughly in various weight ratios (*i.e.* 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, 9:1) respectively. Phase diagrams were constructed using aqueous titration method. In the phase diagrams, only emulsion points were plotted (shaded area), so that there is no overcrowding of the points. In order to prepare SNEDDS, the selection of nanoemulsion region from the phase diagram was based on the fact that solution remains clear even on infinite dilution [11].

Formulation of L-SNEDDS: From the pseudo-ternary phase diagrams, the different oil ratios: Smix were selected, and the drug was incorporated by solubilizing in oil phase. The formulation of L-SNEDDS is given in **Table 1**.

TABLE 1: FORMULATION OF L-SNEDDS

Formulation code	Smix Ratio	Oil:Smix	Drug (mg)	Oil	Surfactant	Co-surfactant
			Famotidine	Oleic acid (ml)	Tween 20 (ml)	Transcutol-P (ml)
F1	1:2	1:9	100	0.5	3	6
F2	1:2	2:8	100	1.5	2.66	5.33
F3	1:2	6:4	100	5.5	1.33	2.66
F4	1:3	2:8	100	1.5	2	6
F5	1:3	4:6	100	3.5	1.5	4.5
F6	1:3	3:7	100	2.5	1.4	5.6
F7	1:3	6:4	100	5.5	1	3
F8	1:4	3:7	100	2.5	1.4	5.6
F9	1:4	4:6	100	3.5	1.2	2.8
F10	1:4	5:5	100	4.5	1	4
F11	1:1	1:9	100	0.5	4.5	4.5
F12	1:1	2:8	100	1.5	4	4
F13	1:1	4:6	100	3.5	3	3
F14	1:1	7:3	100	6.5	1.5	1.5
F15	2:1	2:8	100	1.5	5.33	2.66
F16	2:1	3:7	100	2.5	4.66	2.33

F17	2:1	4:6	100	3.5	4	2
F18	3:1	1:9	100	0.5	6.75	2.25
F19	3:1	2:8	100	1.5	6	2
F20	3:1	3:7	100	2.5	5.25	1.75
F21	4:1	6:4	100	5.5	3.2	0.80
F22	4:1	5:5	100	4.5	4	1

Evaluation Parameters of Famotidine loaded L –SNEDDS:

Thermodynamic Stability Studies: The Stability studies help in assessing the effect of change in temperature on the L-SNEDDS formulations. For centrifugation stress, the L-SNEDDS formulations were diluted with an aqueous phase and centrifuged at 3500 rpm for 15 min and visually observed for any phase separation. Further, the formulations were subjected to heating and cooling cycles for about six cycles between the refrigerator, 40ºC and 45ºC with storage at each temperature for not less than 48 hr was studied [12, 13].

Visual Observation and Phase Separation: Visual assessment was performed by dropwise addition of the preconcentrate (SNEDDS) into 250 ml of distilled water. This was done in a glass beaker at room temperature, and the contents were gently stirred magnetically at ~100 rpm. Precipitation was evaluated by visual inspection of the resultant emulsion after 24 h. The formulations were then categorized as clear (transparent or transparent with a bluish tinge), nonclear (turbid), stable (no precipitation at the end of 24 hours), or unstable (showing precipitation within 24 hours). It gives information about the stability and viability of the formed microemulsion [14].

Robustness to Dilution: It was studied by diluting the liquid SMEDDS to 10, 100, and 1000 times with water and 0.1N HCl solution. It was observed for any phase separation and drug precipitation [15].

Self-emulsification Time: Self-emulsification time enables in determining the efficiency of self-emulsification of the formulation. This test is performed using dissolution apparatus USP type II in which 2.1ml of each formulation was added dropwise to the basket containing water or 0.1 N HCl maintained at 37±0.5ºC and paddle rotating at 50 rpm and was observed visually for assessment of self-emulsification [1, 16].

Dispersibility Test: The efficiency of dispersibility was assessed by using a USP XXII dissolution apparatus II. Each formulation (0.5 ml) was added to 500 ml distilled water maintained at 37±0.5°C, with paddle rotating at the speed of 50 rpm for gentle agitation. The *in-vitro* performance of the formulations was visually assessed using the grading system [11, 17]. (Grade A: Rapid forming, clear and transparent emulsion; Grade B: Rapid forming, less clear, bluish-white appearance emulsion; Grade C: Bright white emulsion or grayish-white emulsion with a slight oily appearance that is slow to emulsify; Grade D: Exhibit poor or minimal emulsification with large oil droplets present on the surface).

Determination of Drug Content: The drug content was determined by performing an assay of liquid SNEDDS. Formulation containing famotidine equivalent to one dose was added to 10 ml methanol, sonicated, and extracted. The extracted solution was suitably diluted with 0.1NHCl, filtered using Whatman filter paper. The content was estimated by UV spectrophotometry at 266 nm using standard curve [11].

***In-vitro* Drug Dissolution:** *In-vitro* drug release behaviour of drug from pure famotidine and L-SNEDDS dispersion was determined using a modified dialysis method in USP type II dissolution apparatus. On oral administration, L-SNEDDS form o/w emulsion when they come in contact with gastric media/aqueous. At this stage, the drug exhibits several different complex states such as molecular state, micellar solution, and entrapment in emulsion globules. Hence, the dialysis bag method was used soaked in freshly prepared 0.1 N HCl medium for 12 h at room temperature. L-SNEDDS formulation and pure drug equivalent to one dose was filled inside the dialysis bag and both the ends of dialysis bags were sealed tightly without any leaks and were dropped into 900 ml of dissolution media maintained at 37ºC and rotated at 50 rpm. Samples (5ml) were withdrawn at time intervals of 5mins, 10mins, 15min, 30min, 45min, and 60min. Replacement with fresh media was done and the samples were

filtered. The concentration of drug was determined by UV-spectrophotometer at 266nm [18, 19].

Droplet Size Measurement: Mean globule size, polydispersibility index (PDI) of the emulsion of optimized liquid-SNEDDS formulations were analyzed on 100 times dilution with double distilled water (100 ml) using a Zetasizer [18].

Zeta Potential: Zeta potential was measured by photon correlation spectroscopy using Zetasizer (Nano ZS, Malvern Instruments, UK) equipped with 4.0 mW He-Ne red laser (633 nm), which measures the potential ranged from −120 to 120 V. Optimized liquid SNEDDS formulation was diluted with double distilled water (100 mL) for the measurement of zeta potential at 25°C [20].

Conversion of L-SNEDDS to S-SNEDDS: The optimized liquid SNEDDS F1, F19, was selected based on several evaluation tests and *in-vitro* drug release. The liquid SNEDDS was converted into solid SNEDDS by mixing the liquid formulation to the pharmaceutical grade adsorbent and converted into a free-flowing powder.

Prosolv SMCC 50 (silicate microcrystalline cellulose), Neusilin US2 (Amorphous Magnesium alumino-metasilicate), and Fujicalin (Dibasic Calcium phosphate anhydrous) were used as solid carriers. The free-flowing powder was filled into size "0" capsules.

Holding Capacity of Adsorbents: The appropriate amounts of carrier & coating material used for each formulation depends on the loading factor (Lf) of the formulation. The L-SNEDDS formulations were taken, and a calculated amount of carrier was added by continuous mixing in a mortar. The adsorbent was added till the contents looked dry. Lf is calculated based on the carrier adsorbed by formulation [21].

$$Lf = W/Q$$

Where; W=L-SNEDDS formulation, Q= carrier material

Evaluation of Flowability and Compressibility of the Powder: The flowability of the obtained powders, after determining the holding capacity of the excipients, was calculated by measuring the angle of repose (direct method).

Determination of bulk density and tapped densities of the obtained mixtures was used to calculate both the Hausner ratio and the compressibility index [22].

Angle of Repose: The solid carrier was chosen based on its angle of repose (flow property). The funnel method proposed by Newman was used to assess the angle of repose. 0.4ml of liquid-SNEDDS was added to increasing amounts of the solid carrier until the mixture became free-flowing and passed through the funnel which was maintained at the height of 1 cm. Angle of repose is determined by using the following formula.

$$\text{Tan } \Theta = h/r$$

$$\text{Therefore } \Theta = \text{Tan}^{-1}h/r$$

Where Θ = Angle of repose, h =Height of cone, and r = radius of the cone base

Bulk Density: Bulk density, ρ_b, is defined as the mass of the powder divided by the bulk volume [21].

$$\rho_b = \text{Weight in gms} / V_b \text{ (bulk volume)}$$

Tapped Density: Tapped density, ρ_t, is defined as the mass of the powder divided by the tapped volume [21].

$$\rho_t = \text{Weight in grams} / Vt \text{ (tapped volume)}$$

Compressibility Index: Carr's index was calculated from the following equation using the values of bulk density (ρ_b) and tapped density (ρ_t) obtained in the earlier experiments[21].

$$C = (\rho_t - \rho_b / \rho_t) \times 100$$

Hausner Ratio: Hausner ratio is an indirect index of ease of powder flow. It is calculated by the following formula

$$\text{Hausner ratio} = \rho_t / \rho_b$$

Where ρ_t is tapped density and ρ_b is bulk density. Lower Hausner ratio (<1.25) indicated better flow properties than higher ones [21].

Compatibility of Excipients with Capsule Shell: This test was performed to check the compatibility of the excipients (oleic acid, Tween 20, and Transcutol-P) with the hard gelatin shell. The capsules were filled with L-SNEDDS adsorbed onto Neusilin US2 and placed at different

temperatures of 40ºC, 60ºC, room temperature, and also in the desiccator (humid condition), which was saturated using calcium chloride and potassium chloride solution. All the capsules filled with formulation and plain capsules were sealed in an airtight self-sealing pouch and placed inside a glass bottle at the conditions mentioned earlier for one week and observed for any weight variation, swelling, and color change.

Evaluation of S-SNEDDS (Capsules):

Drug-Excipient Compatibility Studies: FTIR spectra of pure drug Neusilin US2, optimized solid SNEDDS were performed using KBr pressed pellet technique. This study illustrates any interactions between the excipients used in physical mixture and pure drug. IR grade dry KBr and sample were added in a glass motor and mixed gently, pressed into a pellet by applying 5.5 metric tons using hydraulic press. The pellet/disc is placed in the FTIR sample holder and scanned over a wavenumber range of 4000 to 400 cm^{-1} [18].

Weight Variation: 20 intact capsules were individually weighed, and the average weight was determined. No individual capsule must fall out of the limits; the acceptable percentage deviation is ±10% of the average weight.

Capsule Lock Length: L-SNEDDS adsorbed onto Neusilin US2 was filled into the capsule and then locked. The capsule length was evaluated before and after the filling process using a screw gauge. This test is performed to ensure proper fit of head into the body when locked, and no overfilling of the content has been done.

Drug Content: The drug content was determined by performing an assay of solid SNEDDS. 20 capsules were randomly selected, and the contents were emptied from the shell. Formulation containing famotidine equivalent to one dose (40mg) was added to 100 ml methanol and sonicated. The extracted solution was suitably diluted (0.1N HCl) and filtered using Whatman filter paper. The content was estimated by UV spectrophotometry at 266 nm using standard curve[11].

***In-vitro* Dissolution Studies:** *In-vitro* drug release study of Solid SNEDDS was performed using USP dissolution apparatus type II. 900 ml of 0.1N HCl was filled in the baskets, and paddle was rotated at 50 rpm, and 37±0.5°C was maintained. 0.4 ml of F1 and F19 soild SNEDDS (containing 40 mg of famotidine adsorbed on Neusilin US2) was filled in hard gelatin capsules. To avoid floating of capsules, sinkers were used. Samples (5ml) were withdrawn at regular time intervals (5, 10, 15, 20, 30, 45, and 60 min), and aliquot amount of 0.1 N HCl was replaced every time. The release from solid SNEDDS formulation was compared with pure drug. The samples were analyzed for the drug content using a UV-spectrophotometer at the wavelength of 266nm.

***Ex-vivo* Permeation Studies:** Preparation of tissue: Ethical clearance for the usage of goat intestine was obtained from IAEC (Institutional Animal Ethics Committee). Freshly slaughtered goat gut was obtained, and the intestine was washed several times with normal saline to clear the contents of the gut. Formulations were filled into the intestinal portion of the gut, and a sac was made by tying the open ends. *Ex-vivo* drug permeation studies of optimized solid SNEDDS F19, liquid SNEDDS, and the pure drug were performed in USP-II dissolution apparatus through goat intestine over a period of 1hr in 0.1 N HCl at 37 ± 0.5˚C with the agitation of paddle at 50 rpm. Samples were collected at predetermined time intervals of 5min, 10 min, 15min, 30 min, 45 min, and 60 min. Fresh media was replaced into the media basket after every sampling. Samples were filtered, and drug content was estimated using UV-spectrophotometer at 266nm[23].

XRD Studies: XRD was performed for optimized solid SNEDDS and pure drugs to study the crystalline nature of the optimized formulation. D-5000 Siemens X-ray diffractometer using Copper K α (1.5406 A°) radiation was used to perform XRD. The data were recorded over a scanning 2θ range of 5° to 50° at a step time of 0.045 steps/0.5 sec and the appearance of new peaks and intensity of the peak was noted. The diffractograms of the optimized S-SNEDDS mixture were superimposed with that of pure drug [24, 25].

DSC Studies: Differential scanning calorimeter studies are performed to analyze the thermal characteristics of the drug along with excipients and for the optimized solid SNEDDS formulation.

This study is performed to observe the drug conversion from crystalline to its amorphous form in the optimized formulation. The DSC scans were recorded at a heating rate of 10℃/min from 25℃ to 250℃ under a nitrogen flow (100ml/min). DSC analysis was performed using Q-1000 TA Instruments Perkin-Elmer Pyris differential scanning calorimeter (DSC). The instrument was calibrated with indium standard. 3-5mg samples were weighed and placed in closed, hermetic sample pans with a pinhole. Samples were heated from 0℃ to 210.0℃. The melting point, heat of fusion, disappearance of the sharp crystalline peak of the drug, and appearance of any new peak and peak shape were noted. The thermogram of the optimized S-SMEDDS formulation was superimposed with that of pure drug [2, 24].

SEM: The surface morphology of F19 L-SNEDDS was determined using an analytical scanning electron microscope (Hitachi S-5200, Japan. Magnification: 20 x to 3,00,00 x). The samples were dispersed in double-distilled water, and a drop was placed on a double adhesive tape stuck to an aluminum stub. The stubs were then coated with platinum to a thickness of about 10 Å under an argon atmosphere using a gold sputter module in a high vacuum evaporator. The stubs containing the coated samples were placed in the scanning electron microscope chamber [26].

Accelerated Stability Studies: SNEDDS filled in hard gelatin capsules are generally susceptible to leakage or hardening of the shell due to the migration of co-solvents/co-surfactants. The optimized formulation filled in capsules were enveloped in an aluminum foil and placed in amber colored bottles and were subjected to stability studies at 40°C±2°C/75%±2% RH for two months. The capsules were evaluated for their physical appearance, percentage release and drug content [27, 28].

RESULTS AND DISCUSSION: From the results of solubility studies, famotidine drug was more soluble in oleic acid (oil), Tween 20(surfactant), Transcutol P (Co-surfactant) as shown in the **Table 2**. Hence oleic acid is selected as the oil phase, Tween 20 as surfactant which also acts as a permeation enhancer and Transcutol P as co-surfactant for further studies due to their emulsification ability for optimum SNEDDS with improved drug loading capabilities.

TABLE 2: SOLUBILITY OF FAMOTIDINE IN OILS, SURFACTANTS, CO-SURFACTANTS

Oils	Amount of Drug (mg/ml)
Sunflower Oil	0.691
Oleic acid	15
Castor Oil	8.598
Arachis oil	0.719
Surfactants	**Amount of Drug (mg/ml)**
Tween 20	38.41
Tween 60	3.537
Tween 80	2.448
Span 20	9.602
Span 80	3.44
Triton X-100	28.5
Co-Surfactants	**Amount of Drug (mg/ml)**
Transcutol P	2.593
PEG 400	1
PEG 600	0.705

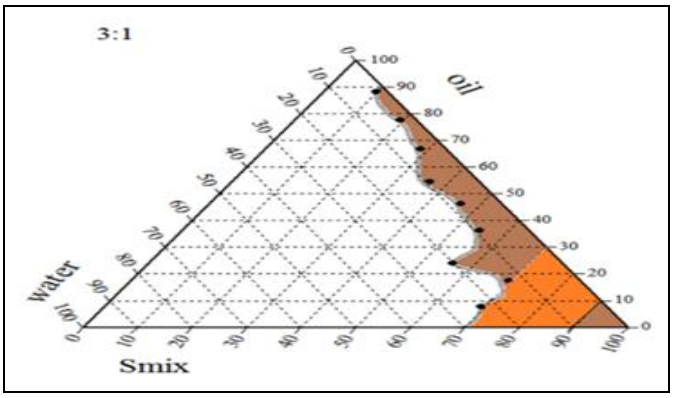


FIG. 1: TERNARY PHASE DIAGRAM OF OLEIC ACID, TWEEN 20, TRANSCUTOL P AT KM VALUES (3:1)

Pseudo ternary phase diagram is used as a tool to identify the zone of emulsification. Phase diagram was constructed using nine different ratios of oleic acid (oil) and mix of Tween 20 (surfactant) and Transcutol-P (co-surfactant) to locate the o/w emulsion zone. The optimum concentration of oil: Smix (surfactant: co-surfactant) was found using CHEMIX software as shown in **Fig. 1**. Each ratio of oil: Smix was titrated with water and agitated for formation of SNEDDS. The oil phase entraps the lipophilic drug and the non-polar tail of surfactant is oriented towards the oil phase whereas the polar head orients itself towards the aqueous phase thus lowering the surface tension between both the phases. The other factor responsible for formation of micro-emulsion is the surfactant to co-surfactant ratio. The hydrophilic co-surfactant in conjunction with surfactant absorbs at the interface and fluidizes the hydrocarbon region resulting in continuous formation of micro-emulsion and also stabilizing it. Thus, selection of the excipients and their mixing ratios forms a crucial part in formation

of the micro-emulsions. The pseudo ternary phase diagrams were constructed at the ratios of 1:1, 2:1, 3:1, 4:1 initially, then it was checked for formulation of emulsion and the surfactant ratio is fixed.

The emulsions formulated using ternary phase diagrams were subjected to various tests to assess the physical stability of the SNEDDS and observe for any drug precipitation. Results of thermo-dynamic stability studies have been summarized in **Table 3**.

It was found that F1, F2, F11, F12, F15, F16, F18, F19, F20 formulations have passed the heating–cooling cycle, no physical separation or cracking of the SNEDDS has been observed in the formulations that passed the study. Formulation F2, F12 have shown drug precipitation at high temperatures.

The samples were visually observed for any physical separation or precipitation of drug for 48 hours and F1, F2, F11, F12, F15, F16, F18, F19, F20 have exhibited the highest stability without any separation of phase or drug precipitation as mentioned in **Table 3**.GI fluid volume exhibits higher inter-subject variability particularly in case of fed and fasted states. The success of SNEDDS formulation depends on the ability to form microemulsion even at infinite dilution, as the process of dilution by the GI fluids lead to gradual desorption of surfactant located at the globule interface. There was no sign of phase separation or drug precipitation on dilution in formulations F1, F11, F12, F15, F16, F18, F19, and F20 as given in **Table 3** [15].

Almost all the formulations have emulsified within 180 sec. Formulations F1, F11, F15, F18, F19, and F20 have shown emulsification time of less than one min which are mentioned in **Table 3**. These samples were further preceded for the dispersiblity test.

Formulations F1, F11, F18 have exhibited grade A by forming rapid emulsion with transparent appearance, grade B was exhibited by formulations F12, F15, F19, F20 with rapid emulsification and bluish white appearance, grade C was exhibited by formulations F2, F4, F6, F7, F16 by forming bright white or grayish emulsion and the rest of the formulations exhibited grade D with the presence of oil globules at the surface with poor emulsification. The results are given in **Table 3**.

TABLE 3: RESULTS OF THERMODYNAMIC STABILITY, ROBUSTNESS TO DILUTION, DISPERSIBILITY TEST, AND EMULSIFICATION TIME

Formulation code	Heating & Cooling cycle	Centrifugation	Robustness	Dispersibility test	Emulsification time (sec)	Inference
F1	Pass	✓	✓	A	30	Passed
F2	Pass	x	x	C	100	Failed
F3	Fail	x	x	D	134	Failed
F4	Fail	x	x	C	84	Failed
F5	Fail	x	x	D	124	Failed
F6	Fail	x	x	C	80	Failed
F7	Fail	x	x	C	100	Failed
F8	Fail	x	x	D	133	Failed
F9	Fail	x	x	D	141	Failed
F10	Fail	x	x	D	130	Failed
F11	Pass	✓	✓	A	24	Passed
F12	Pass	✓	✓	B	36	Passed
F13	Fail	x	x	D	145	Failed
F14	Fail	x	x	D	131	Failed
F15	Pass	✓	✓	B	66	Passed
F16	Pass	✓	x	C	70	Failed
F17	Fail	x	x	D	127	Failed
F18	Pass	✓	✓	A	58	Passed
F19	Pass	✓	✓	B	42	Passed
F20	Pass	✓	✓	B	56	Passed
F21	Fail	x	x	D	140	Failed
F22	Fail	x	✓	D	137	Failed

The drug content of the formulations was determined using UV-spectrophotometry at 266 nm. F1 and F19 have exhibited 100% drug content.

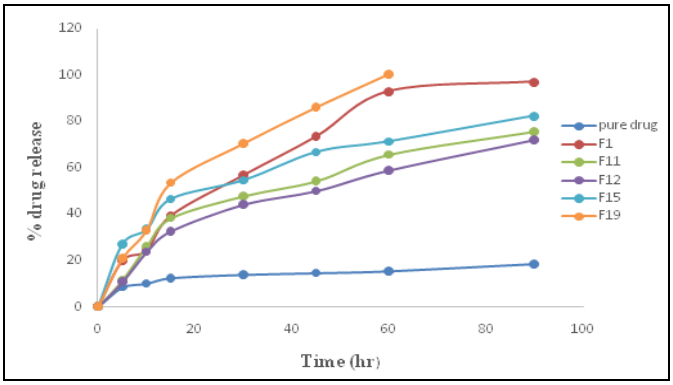


FIG. 2: *IN-VITRO* DRUG DISSOLUTION OF L-SNEDDS IN COMPARISON WITH PURE DRUG

In-vitro drug release studies were performed in USP–II dissolution apparatus with a dialysis membrane. The dissolution studies have been performed, and formulations F1 and F19 have shown a higher rate of percentage release when compared to the pure drug and other formulations. F1 has shown 97% drug release in 90 mins and F19 has shown 100% release within 60 mins.

Among all the formulations, F19 Smix (2:6) and oil: Smix (3:1) has shown a greater cumulative percentage release when compared to the pure drug, as shown in **Fig. 2**.

The particle size distribution of particles is expressed in PDI. Ideally, SNEDDS must display a wide distribution in less than 150 nm; PDI should be less than 0.5. Droplet size distribution forms one of the crucial characteristics of emulsion for stability evaluation and plays a key role in enhancing drug bioavailability; F19 has shown a particle size of 102nm and PDI of 0.36 **Fig. 3** from which it can be inferred that nano range emulsion has been formulated and the particle size possess large interfacial surface area for drug absorption.

Zeta potential is useful in knowing the surface charge of the particle, which can determine its stability. Zeta potential can be either positive or negative; stable formulations may possess a +30 to -30 mV charge. The formulation has shown a Zeta potential of -12.2 mV. The result has been shown in **Fig. 4** [16].

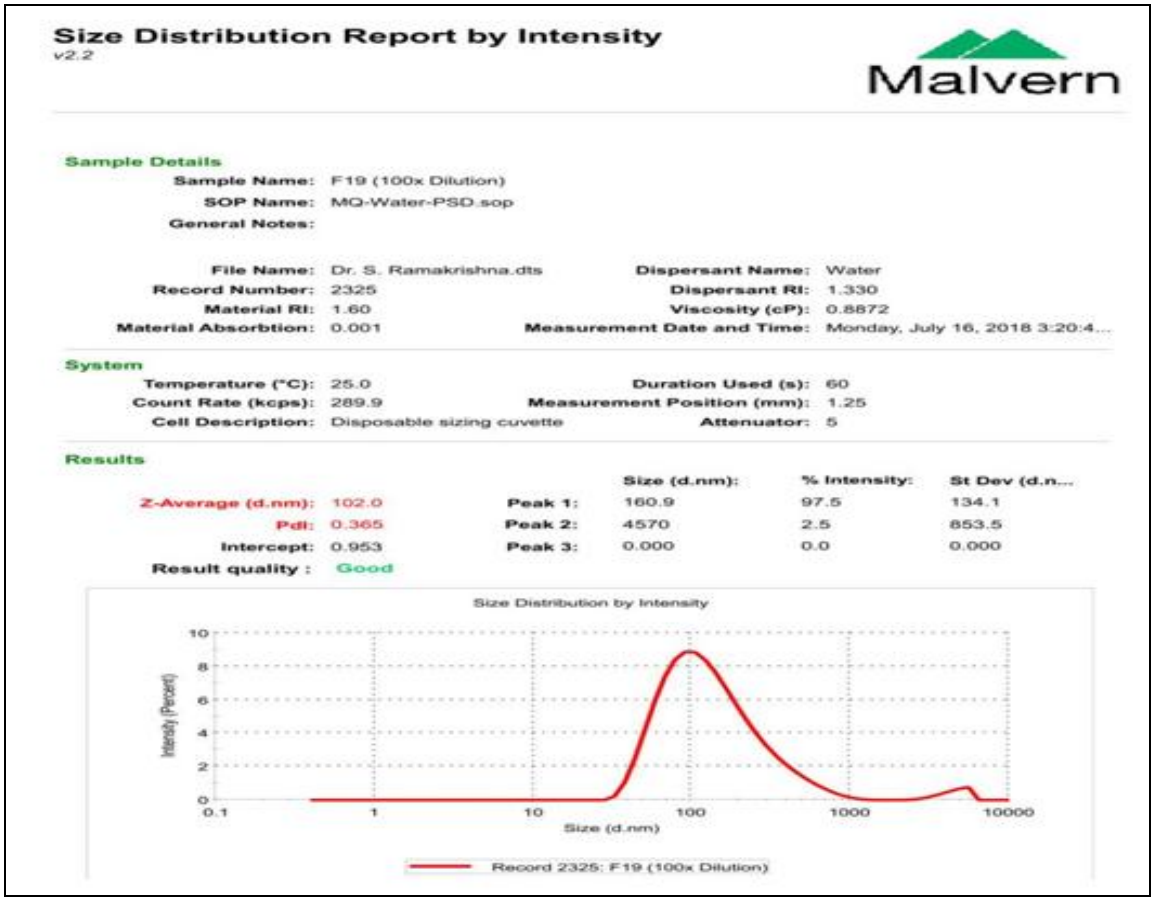


FIG. 3: DROPLET SIZE ANALYSIS OF F19 L-SNEDDS

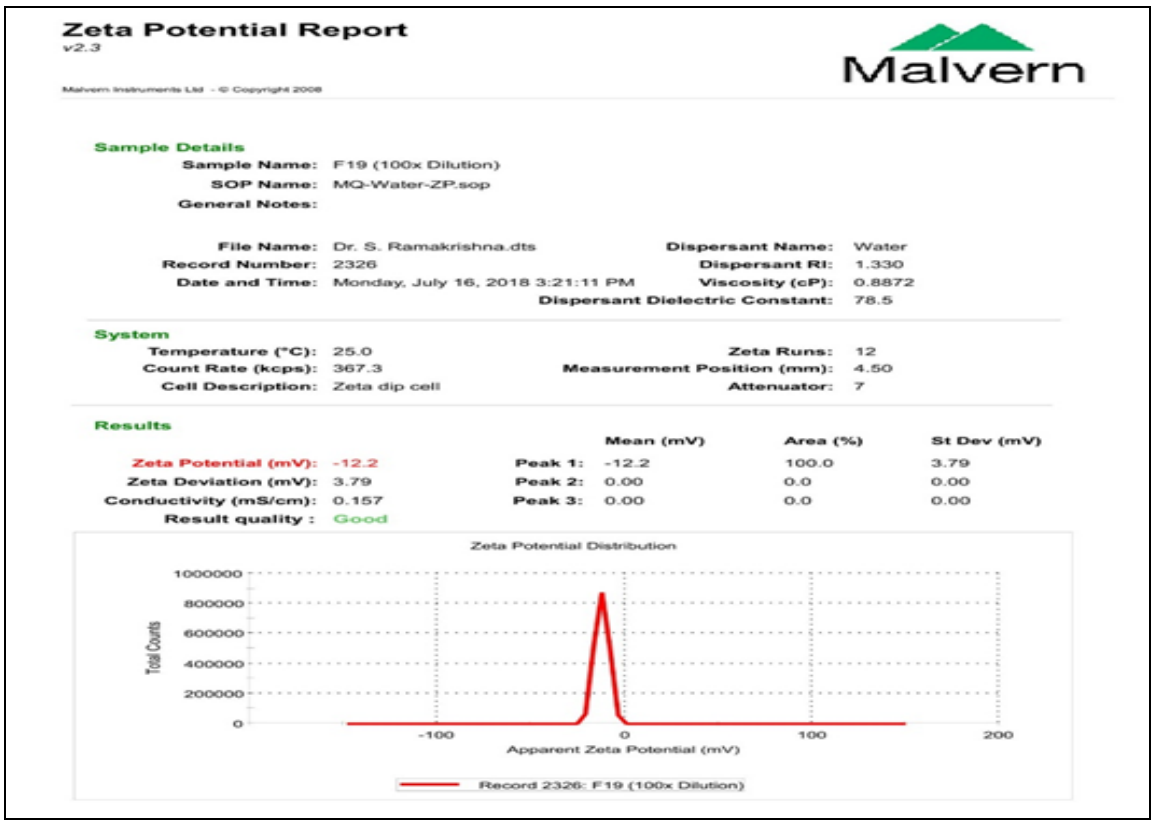


FIG. 4: ZETA POTENTIAL OF F19 L-SNEDDS FORMULATION

The optimized liquid SNEDDS (F1, F19) based on the evaluation and in-*vitro* dissolution studies were converted into free-flowing powder by adsorption onto solid carriers

The solid-SNEDDS containing Neusilin US2 exhibited good flowability and loading of liquid SNEDDS at a lower quantity. Neusilin US2 possesses very small particles and a high surface area which enables absorption of higher amounts of oil onto the solid adsorbent. 180mg of Neusilin US2 was considered as it has shown good flow property when compared to 100mg and 150mg. Fujicalin was not optimized, as its weight was very high to be accommodated in a size "0" capsule though, it exhibited a good flow property. Prosolv was also not considered further as the weight was very high, and it exhibited poor flow property. The amount of carrier to be used in the formulation was calculated by the holding capacity and the Lf factor, as shown in **Table 4**.

TABLE 4: LOADING FACTOR OF OPTIMIZED L-SNEDDS

S. no.	Carrier Material	Carrier Material (Q)		L-SNEDDS (W)		Flowability (°)		Lf= W/Q	
		F1	F19	F1	F19	F1	F19	F1	F19
1	Neusilin US2	100mg	100mg	0.4 ml (409mg)	0.4ml (419mg)	41	40.5	9.97	10.34
		150mg	150mg	0.4 ml (409mg)	0.4ml (419mg)	37	35.5	11.05	11.52
		180mg	180mg	0.4 ml (409mg)	0.4ml (419mg)	32	31.5	12.78	13.3
2	Fujicalin	400mg	400mg	0.4ml (409mg)	0.4ml (419mg)	41	39	9.97	10.7
		450mg	450mg	0.4ml (409mg)	0.4ml (419mg)	38	37.5	10.76	11.17
		480mg	450 mg	0.4ml (409mg)	0.4ml (419mg)	35	35.5	11.68	11.80
3	Prosolv SMCC 50	820mg	800 mg	0.4ml (409mg)	0.4ml (419mg)	-	-	-	-

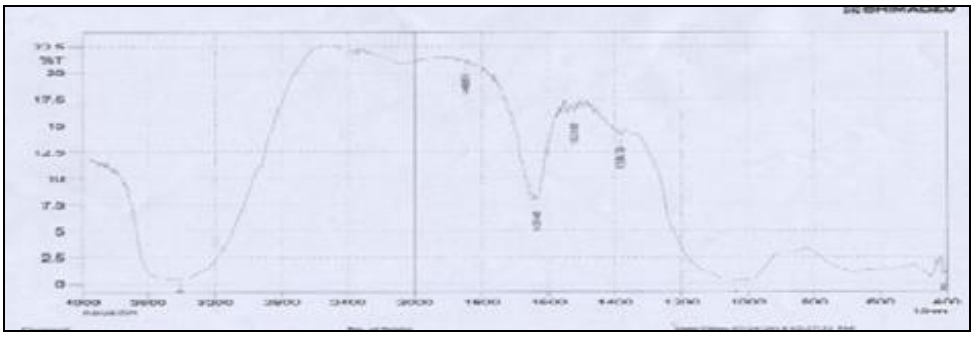
Liquid SNEDDS (F1, F19) was adsorbed on the solid carrier Neusilin US2 and was filled in a capsule of size "0". The angle of repose was found to be between 31.5±0.05 to 32±0.19, which indicates a good flow property. Formulations also exhibited an excellent Hausner's ratio between 1.06±0.13 to 1.12±0.16, Hausner's ratio lower than 1.2 indicates good flow, and if the ratio is more than 1.2, it indicates bad flow. Compressibility was also found to be good, the percentage being between 6.45±0.33 to 11.42±0.23[29]. The results are given in **Table 5**.

TABLE 5: FLOWABILITY AND COMPRESSIBILITY PROPERTIES OF SOLID-SNEDDS

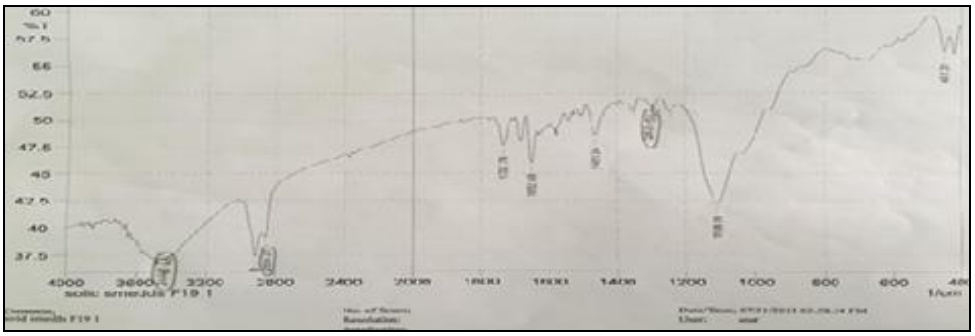
Formulation code	Angle of repose (θ)	Bulk Density (gm/cm^3)	Tapped Density (gm/cm^3)	Hausner Ratio	Compressibility Index (%)
Solid F1	32±0.19	0.29±0.16	0.31±0.32	1.06±0.13	6.45±0.33
Solid F19	31.5±0.05	0.31±0.23	0.35±0.11	1.12±0.16	11.42±0.23

Compatibility studies with capsule shells were performed as per the procedure mentioned in the experimental methodology. There was no alteration in the physical appearance and weight of the capsule filled with powder F19 SNEDDS (liquid SNEDDS adsorbed on to Neusilin US2). Thus, it can be concluded that the excipients and the quantity used in the formulation do not have any interaction with the shell. The plain capsule was found to be an initial weight variation of 0.132±0.2mg and final weight variation of 0.132±0.5mg, and capsule with powder F19 was found to be initial weight variation of 651±0.26mg and a final weight variation of 651±033mg.

DRUG



NEUSILIN US2



SOLID SNEDDS F19

FIG. 5: FTIR SPECTRUM OF PURE DRUG, NEUSILIN-US2 AND SOLID-SNEDDS F19

IR was performed to know if there was any interaction between the pure drug and various excipients used in formulations. The solid SNEDDS sample containing the liquid SNEDDS (oleic acid, tween 20, and transcutol-p) and solid adsorbent NeusilinUS2 were recorded by KBr pellet method using IR spectrophotometer in the range of 400-4000cm^{-1} and compared with the spectrum of pure drug of famotidine. **Fig. 5** represents the spectrum of pure drug, Neusilin-US2 and solid-SNEDDS F19.

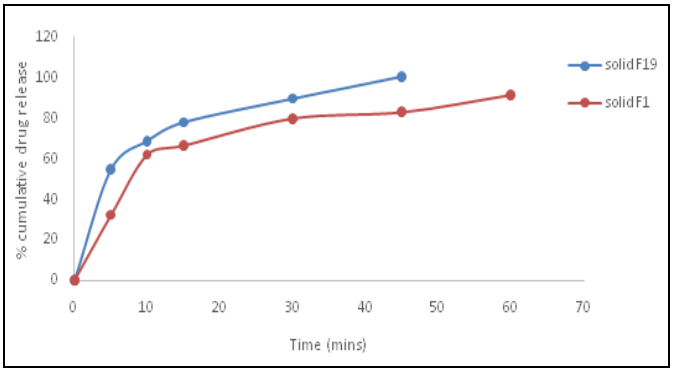


FIG. 6: *IN-VITRO* DRUG DISSOLUTION OF SOLID SNEDDS CAPSULES

Ex-vivo intestine permeation studies were performed in USP type II dissolution apparatus as per the procedure. The permeation across the goat intestine of the pure drug was found to be 44±0.08%, permeation of F19 liquid SNEDDS was found to be 98±0.13%, and the solid-SNEDDS has shown a drug permeation of 96.98±0.1 % in 120 mins. **Fig. 7** depicts the permeation profile. The liquid-SNEDDS has shown a higher permeation rate than solid-SNEDDS due to its nano size and higher surface area of globules in the microemulsion. Usage of Tween 20 might have led to opening of tight junction and better drug permeation of the drug.

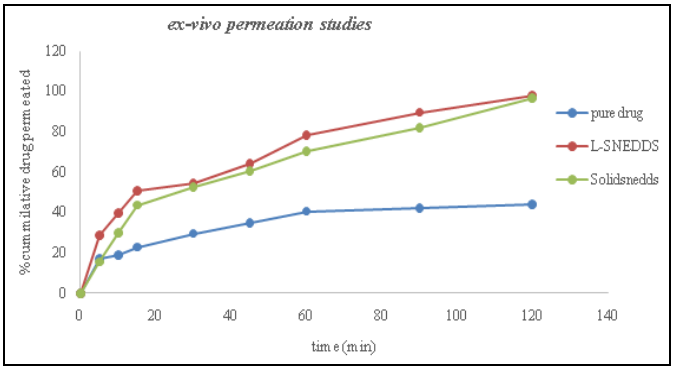
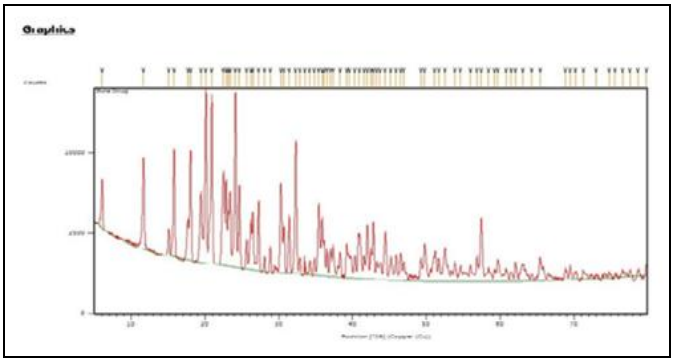
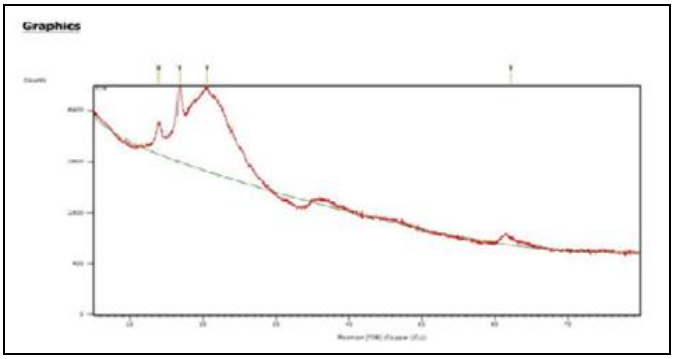


FIG. 7: *EX-VIVO* PERMEATION STUDIES OF PURE DRUG, L-SNEDDS AND SOLID-SNEDDS (F19)

The change in the degree of crystallinity of the prepared S-SNEDDS was studied by XRD. The pure drug and optimized formulations were also analyzed by XRD in a similar manner, and the presence of new peaks and peak intensity was observed. The X-ray diffraction pattern of famotidine exhibited sharp, highly intense, and less diffused peaks indicating the crystalline nature of the drug as shown in **Fig. 8**. The XRD of optimized formulation S-SNEDDS formulation (solid-F19) displayed decreased peak intensity in comparison to the pure drug, and it may be due to complete solubilization or amorphization of famotidine in the SNEDDS, which can consequently contribute to enhancement in the dissolution, solubility, and bioavailability of famotidine.



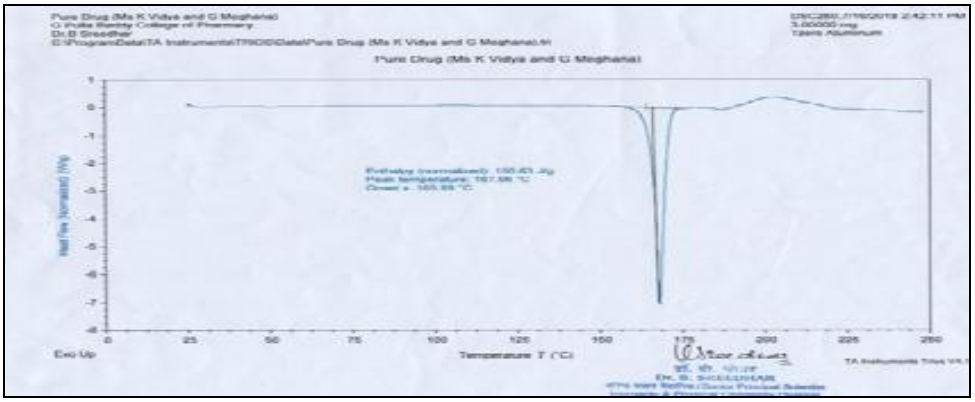
PURE DRUG



SOLID SNEDDS F19

FIG. 8: XRD PATTERN OF PURE DRUG AND SOLID-SNEDDS F19

DSC thermogram **Fig. 9** demonstrating a sharp characteristic endothermic peak at 165.99 ˚C, which corresponds to its melting temperature, which signifies the presence of famotidine (pure drug) in its crystalline form. The DSC thermogram of the optimized solid- SNEDDS F19 displayed a broad peak at 81.76 ˚C and total disappearance of famotidine peak, which may be due to the complete conversion of the pure drug into its amorphous state in the final formulation [30, 31].



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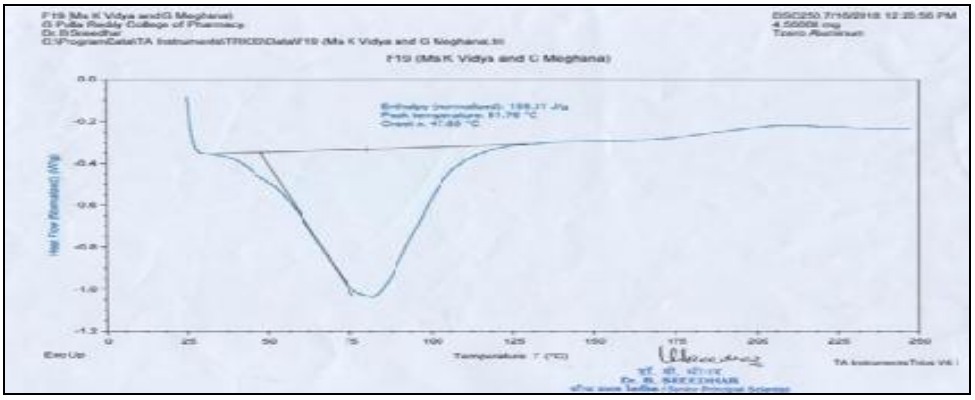

SOLID SNEDDS F19

FIG. 9: DSC OF PURE DRUG AND SOLID-SNEDDS F19 FORMULATION

The surface morphology of the solid SNEDDS powder was examined by SEM. Image is given in **Fig. 10**, which shows liquid SNEDDS is adsorbed onto adsorbent and result in lumps or powder.

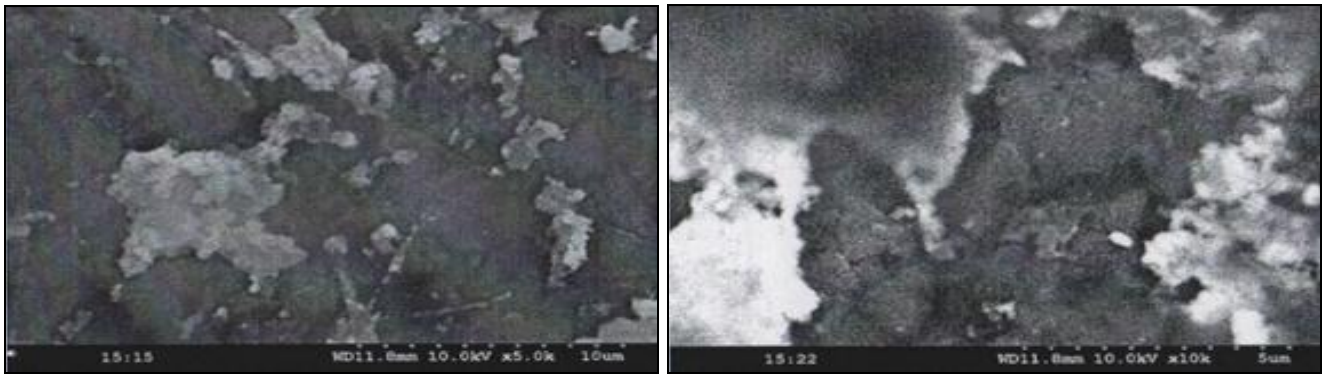

FIG. 10: SEM OF SOLID-F19 FORMULATION

The Neusilin-SNEDDS (F19) formulation was filled into hard gelatin capsules as the final dosage form. According to the accelerated stability studies given in experimental methodology, stability studies at 40°C±2°C/75%±2% RH for a period of two months was performed. **Table 6** shows that the formulation has not shown any alteration in physical appearance and complies with official specifications.

TABLE 6: STABILITY STUDY OF OPTIMIZED FORMULATION SOLID SNEDDS F19

	time		
Parameters	**0 (Initial)**	**1st Month**	**2nd Month**
Appearance	No change	No change	No change
Drug content (%)	100±0.03	100±0.02	99.89±0.06
Capsule lock length (cm)	No change	No change	No change
Dissolution (%)	100.84±0.01	100.68±0.05	100.12±0.08

CONCLUSION: The present study was to increase the solubility and permeability of famotidine, a histamine H-2 receptor blocker utilizing the approach of solid self nano emulsifying drug delivery systems. It was investigated that this technique would improve the solubility of famotidine since it is a poorly soluble drug (BCS class IV). Based on the solubility studies of famotidine the solvents having maximum solubility include oleic acid (15 mg/ml), Tween 20 (38.41 mg/ml), and Transcutol P (2.593 mg/ml) as the oil, surfactant, and co-surfactant, respectively. Twenty-two formulations were chosen based on the ternary phase diagram, and all the evaluation parameters were done. F1 formulation has shown drug release of 97.15±0.02 in 90 minutes. F19 formulation has shown drug release of 100.23±0.1% in 90 minutes. Both F1 and F19 have shown a higher % of drug release when compared to pure drugs (42.03% in 90 minutes).

The particle size of F19 was evaluated and found to be 102nm and PDI of 0.36, and it has shown uniform particle size distribution. The particle size has shown a negative charge with a zeta potential of -12.2 mv from which it can be concluded that the formulation is stable. The optimized liquid SNEDDS were converted to solid -SNEDDS by using several adsorbents like Neusilin US2, Fujicalin, and Prosolv SMCC 50. Neusilin US2 solid-SNEDDS has shown a good angle of repose of 31.5±0.05°, and the powder is filled into size "0" capsule. *Ex-vivo* studies were performed using the goat intestine, and the permeability was found to be enhanced. Liquid F19 has shown 98±0.13% of drug permeation, and solid F19 has shown 96.98±0.1 % drug permeation in 120 minutes. The optimized formulation of famotidine was characterized by X-ray diffraction, FTIR, and DSC studies. No interaction was observed. XRD data revealed that the formulation showed reduced crystallinity when compared to pure drugs. Stability studies indicate the formulations were stable. In conclusion, it can be stated that the objective of the study was achieved by improving the solubility of famotidine using solid- self-emulsifying drug delivery systems.

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