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Formulation and evaluation of self nano-emulsifying drug delivery system of ezetimibe for dissolution rate enhancement

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ABSTRACT

The present study was aimed to develop a Self Nano Emulsifying Delivery System of Ezetimibe (EZM) for enhancing its dissolution rate. Ezetimibe is a cholesterol absorption inhibitor, being a lipophilic drug due to its low solubility EZM shows a low dissolution profile. The SNEDDS formulation consisted of excipients Cinnamon oil, Tween 80, PEG 400 as the Oil, Surfactant and Co-surfactant. Twelve formulations with different ratios of Oil, Surfactant and Co-surfactant were prepared. The liquid SNEDDS were then converted into Solid form by adsorption technique using Avicel PH 101 and Aerosil 200 as adsorbents. The liquid SNEDDS was characterised for Particle size, Emulsification time, Dispersibility, percentage transmittance, PCM, Centrifugation, Cloud Point and Freeze thaw cycle. The solid form was characterized for the flow property, SEM, Drug content and *in-vitro* dissolution. Among the twelve formulations F6 formulation was found to have a particle size of 196 nm and PDI of 0.123. F6 formulation was selected as the best and it was made into solid by adsorption onto solid carriers. The F6 formulation consisted of the 25% Cinnamon oil, 50% tween 80 and 25% PEG 400. The *in-vitro* dissolution rate of the prepared formulation was compared with the marketed formulation. The *in-vitro* dissolution data showed that the drug release at the end of 60 mins from marketed formulation was 63.75 % and from SNEDDS formulation was 90.62 %. The dissolution rate of the prepared SNEDDS was increased by 1.42 times than the marketed formulation. The increase in the dissolution rate shows that SNEDDS is a suitable drug delivery system to enhance the rate of dissolution of Ezetimibe.

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INTRODUCTION

Ezetimibe is a lipid-reducing agent which specifically removes cholesterol and associated phytosterols from the intestinal absorption without influencing the absorption of fat-soluble nutrients, triglycerides or bile salts. As a BCS group II enzyme, Ezetimibe is a strongly lipophilic molecule with a log P value of 4.5 (Drugs, 2020; PubChem-Ezetimibe Compound Summary, 2020). This displays a particularly unstable and weak dissolution profile in the gastrointestinal tract owing to its hydrophobicity. Formulation of BCS class II drugs as SNEDDS has shown to improve the solubility of drugs and thus increase the dissolution of drugs. Self Nano Emulsifying Drug Delivery Systems (SNEDDS) are preconcentrates of nanoemulsion or anhydrous forms of nanoemulsion. These systems are anhydrous isotropic mixtures of oil, surfactants and drugs that spontaneously form O/W nanoemulsions when they

are introduced into aqueous phase under conditions of mild agitation (Savale, 2015). The purpose of this study was to design and evaluate different formulations of S-SNEDDS using various S mix ratios and adsorbent mixtures to achieve an enhancement in the dissolution rate of Ezetimibe.

MATERIALS AND METHODS

Ezetimibe was provided as a gift sample from Medreich Limited, Bangalore, Karnataka, India. Cinnamon oil was brought from S.D. Fine Chemicals, India. Tween 80 (Polyoxyethylene 20 sorbitan mono-oleate), PEG 400 (Polyethylene glycol), Avicel PH 101 (Microcrystalline cellulose) was purchased from Sigma-Aldrich. Aerosil 200 was obtained from Biochemika reagents.

Solubility study

The solubility of Ezetimibe was found by a method of equilibrium solubility and saturation solubility using various oils, surfactants and co-surfactants. To determine the solubility an excess amount of the drug was introduced in to the tubes containing 1 ml of excipient. The vial was shaken continuously and vortexed using vortex mixer (REMI Equipment, Mumbai, India) for few minutes. The mixtures were then equilibrated at room temperature for 48 hrs. The samples were centrifuged (Eppendorf centrifuge 5415 R) at 5000 rpm for 10 mins. From the supernatant, the sample was then dissolved in ethanol to extract the drug and then suitably diluted with distilled water and the EZM dissolved in the oils were quantified using UV spectroscopy method (Nasr *et al.*, 2016).

Screening of surfactants

Different surfactants were screened for their emulsification efficiency. The surfactants used were tween 80, tween 20, span 80, span 20. The solubility was first determined by same procedure as used for oils. Emulsification ability was determined by adding 300 μl of the selected surfactant to 300 μl of the oil phase (1:1 ratio). The mixture was then heated to 50°C and mixed to form a homogenized mixture. 25 μl of the mixture was then diluted to 25 ml with distilled water to form an emulsion.

Screening of co-surfactants

Co-surfactants were selected on the basis of their efficacy to improve the emulsification ability of the chosen surfactants. Co-surfactants like PEG 400, glycerol were used. The mixtures of co-surfactant, surfactant and oil were prepared in the ratio of 1:2:3. It was mixed and heated to form a homogenous mixture. The % transmittance of the mixtures was found out by the same procedure for surfactants (Nasr *et al.*, 2016).

Pseudo ternary phase diagram

The pseudo ternary phase diagram was plotted using the method of water titration. The surfactant and co-surfactant were mixed in different proportions (1:1, 2:1, 3:1, 1:2). To this oil phase was added to this in varying proportions. This mixture was then titrated with water until it turns clear or milky, translucent and free flowing. The values were then plotted in CHEMIX software to obtain the nano emulsion region (Patel *et al.*, 2016).

Formulation of liquid-SNEDDS

Formulations with varying concentrations of oil (20-30%) and Surfactant and co-surfactant mixture (70-80%) were prepared. The required quantity of tween 80 and PEG 400 were measured and added to a glass beaker. It was stirred continuously using a magnetic stirrer (2MLH, REMI Instrument). To this the oil was added and finally, the desired amount of EZM was weighed and added to the mixture. The stirring was continued for around 45 - 60 mins. It was then sonicated (Sonics-230 $\pm$ 10V) for about 20 mins. The prepared L-SNEDDS was stored at room temperature (25°C) in an air-tight container (Nasr *et al.*, 2016). The composition of the SNEDDS formulations are shown in Table 1.

Characterization of L-SNEDDS

Particle Size and PDI

Particle size or globule size determines the rate and extent to which the drug is released and was determined by using Malvern Zeta-sizer (MALVERN Zeta-sizer ZS90) (Patel *et al.*, 2016).

Time for Emulsification

Time for emulsification of the formulations was found out by adding 1 ml of the formulation to 900 ml of distilled water in USP dissolution apparatus II (LABINDIA DS 8000). Stainless steel paddle which rotates at 50 rpm provides the stirring. The time required for the formulation to completely disperse uniformly was noted which was the emulsification time (Patel *et al.*, 2016).

Dispersibility test

The dispersibility test was performed to find out the emulsification efficiency of the formulations. 0.5 ml of the formulation was added to 250 ml of distilled water in a dropwise manner. The test was done in a glass beaker kept on a magnetic stirrer with agitation at around 100 rpm and temperature was maintained at 37$\pm$0.5°C. The solutions were then analysed visually for clarity using a grading system (Kassem *et al.*, 2016).

Grade A – nano emulsion forms rapidly within 1 min, has a clear or bluish appearance.

Grade B – nano emulsion forms within 2 mins, it is less clear and has a bluish appearance.

Grade C – fine milky emulsion forms within 2mins.

Grade D – emulsion was formed after 2 mins. dull, greyish white emulsion and slightly oily in appearance.

Grade E – emulsion was poorly formed which has large oil globules on the surface (more than 3mins).

Percentage transmittance

25 μl of EZM loaded L-SNEDDS was reconstituted with distilled water up to 25 ml to form a nano emulsion. It was observed visually for clarity. The % transmittance of the samples was measured at 650 nm in UV-Vis spectrophotometer (Lalwani *et al.*, 2013).

Effect of dilution

The samples were diluted 100 and 1000 times with water and 0.1 HCl. It was allowed to stand for 24 hours and viewed for any changes such as phase separation or precipitation of drug (Ali and Hussein, 2017).

Characterization of the F6 formulation

Phase Contrast Microscopy

The morphology of the drug loaded F6 liquid SNEDDS was determined by Phase Contrast Microscopy (Leica S40, 230 $\pm$ 10 V, 5 W). The morphology was determined by focusing the lens 10X and 40X.

Cloud point determination

Cloud point evaluates the temperature effect on the phase behaviour of SNEDDS. The sample was diluted in the ratio of 1:250 with distilled water and heated. Cloud Point is the temperature at which there is a sudden appearance of cloudiness. The temperature was noted visually (Patel *et al.*, 2016)

Centrifugation test

The EZM SNEDDS sample was diluted to 100 times using distilled water and the samples were centrifuged (EPPENDROFF, 5415 R, Germany) at 4000 rpm for 30 mins. It was then examined for any instabilities (Kassem *et al.*, 2016; Patel *et al.*, 2016).

Freeze-thaw cycle

Freeze-thaw cycle involves the accelerated stability study of the formulations. It involves three freeze thaw cycles at temperatures -20°C and +25°C kept for 48 hrs. Any instability was observed in the formulation (Kassem *et al.*, 2016).

Formulation of EZM loaded solid SNEDDS

The optimized L-SNEDDS was transformed to solid SNEDDS with the use of porous solid carriers like adsorbents. Adsorption onto the solid carriers is the easiest way to convert the liquid into the solid. The liquid SNEDDS of about 1ml was taken in porcelain dish and different quantities of adsorbents like aerosil, avicel PH 101, lactose, mannitol etc. The adsorbent which had the highest adsorption capacity and good flow properties were chosen as the adsorbent. A combination of Avicel PH 101 and Aerosil 200 was selected for the study (Patel *et al.*, 2016). The solid SNEDDS prepared by adsorption onto carriers were then filled into hard gelatine capsules.

Characterization of S-SNEDDS

Micromeritic properties of powders

It is the study of the fundamental and derived properties of individual as well as a collection of particles.

Bulk Density

Bulk density is the mass per unit volume of a loose powder bed, including the volume of all interparticle voids. Bulk density was calculated using the equation given below (Ali and Hussein, 2017)

$$Bulk\ density\ =\ \frac{M}{V_0}$$

M - Mass in grams.

Vo – Untapped apparent volume in ml (bulk volume).

Tapped Density

Tapped density is the ratio of the mass of the powder to the volume of the powder occupied after it is tapped for a defined period of time. It is expressed in g/ml. It was calculated using the formula (Ali and Hussein, 2017)

$$Tapped\ density\ =\ \frac{M}{V_f}$$

V_f – the final tapped volume in ml.

Hausner's ratio

The hausner's ratio predicts the propensity or flowabilty of a given powder sample to be compressed (Ali and Hussein, 2017). It was determined by the formula

$$Hausner\ ratio\ =\ \frac{V_0}{V_f}$$

Carr's Index

Carr's Index is an indication of the compressibility and flowability of a powder. It is expressed in percentage (Ali and Hussein, 2017). It is calculated

from the formula

$$Carr's\ index\ =\ \frac{100(V_0 - V_f)}{V_0}$$

Angle of Repose

The angle of repose is the angle produced by a heaped cone of a free standing powder. The determination of the angle was done by "poured" angle method (Ali and Hussein, 2017). It is calculated by the formula

$$\theta = \tan^{-1}\left(\frac{h}{r}\right)$$

Where,

θ is the angle.

h - Height of the pile in cm

r – Radius of the pile in cm

FT-IR studies

FT-IR studies was carried out for the drug and final physical mixture by the KBr press pellet technique.

Scanning Electron Microscopy

The size and morphological feature of solid SNEDDS were examined using scanning electron microscopy. The photograph was taken at acceleration voltage of 15KV.

Drug content

Amount of sample equivalent to 10 mg of Ezetimibe is weighed and taken in a standard flask. A little quantity of ethanol is added to dissolve the drug and it is made up to 10 ml with distilled water. It is then further diluted to the desired concentration. Sample absorbance was measured by UV spectroscopy at 236 nm (Lalwani *et al.*, 2013).

In-vitro dissolution

The *in-vitro* dissolution study was performed using USP dissolution apparatus II (LAB INDIA DS 8000). The dissolution test was performed in 0.05 M acetate buffer pH 4.5 with 0.45% SLS (USP, 2018; USFDA, 2008). Volume of the dissolution media was 500 ml. The stirring was provided by paddle rotating at 50 rpm with the temperature at 37±0.5°C. Quantity of the solid formulation equivalent to 10 mg of the drug which was filled in a hard gelatine capsule was added into the medium. The samples were withdrawn at specific time intervals of 10, 20, 30, 45 and 60 min. Absorbance of the samples were then measured using UV spectrometer at 236 nm.

RESULTS AND DISCUSSION

Solubility Study

The amount of drug soluble in the excipients is an important criteria for the formulation of SNEDDS and its stability. The entire dose of the drug being used should be soluble in the excipients. The oil which had the highest solubilisation capacity for the drug was chosen as the oil phase. EZM was found to be highly soluble in cinnamon oil and clove oil. So these two oils were chosen as the oil phase for the further studies. The solubility of Ezetimibe in various excipients are shown Figure 1.

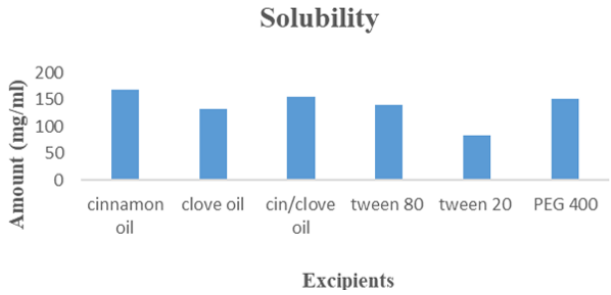

Figure 1: Ezetimibe solubility in various excipients

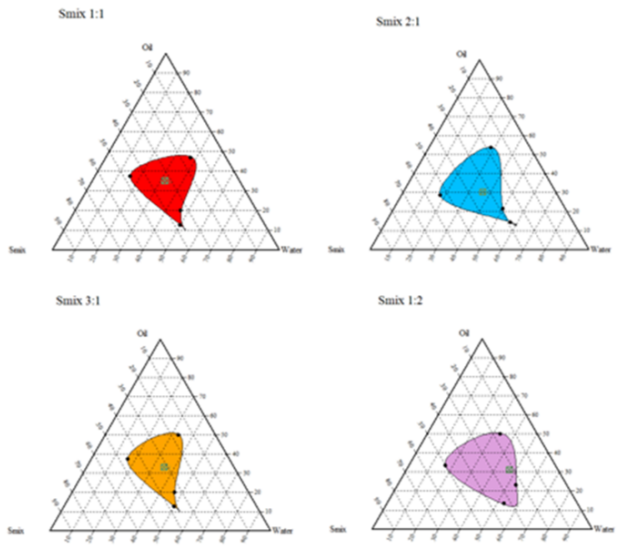

Figure 2: Pseudo Ternary Phase Diagram

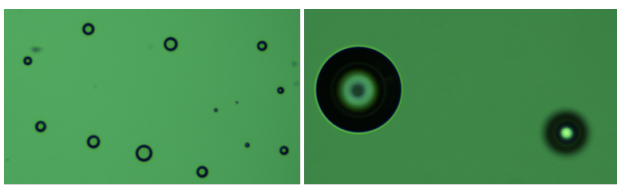

Figure 3: (a) Morphology of L-SNEDDS(10X); (b) Morphology of L-SNEDDS(40X)

Surfactants and co-surfactants screening

The surfactant and co-surfactant were chosen on the basis of their HLB value, emulsifying ability and solubility of the drug in the excipients. The HLB value

Table 1: Composition of Ezetimibe loaded liquid SNEDDS

Formulation	Oil (%)	Smix ratio	Surfactant (%)	Co-surfactant (%)
F1	20	1:1	40	40
F2	20	2:1	53.33	26.66
F3	20	3:1	60	20
F4	20	1:2	26.66	53.33
F5	25	1:1	37.5	37.5
F6	25	2:1	50	25
F7	25	3:1	56.25	18.75
F8	25	1:2	25	50
F9	30	1:1	35	35
F10	30	2:1	46.66	23.33
F11	30	3:1	52.5	17.5
F12	30	1:2	23.33	46.66

Table 2: Percentage transmittance of different mixtures

Composition	No. of flask inversions	% transmittance
Cinnamon oil + Tween 20	19	95.67
Cinnamon oil + Tween 80	19	94.78
Clove oil + Tween 20	16	97.88
Clove oil + Tween 80	16	95.39
Cinnamon oil + Tween 20 + PEG 400	17	97.92
Cinnamon oil + Tween 80 + PEG 400	11	98.05
Clove oil + Tween 20 + PEG 400	12	96.22
Clove oil + Tween 80 + PEG 400	18	96.23

Table 3: Particle size and PDI of the formulations

Formulation	Average Particle size (nm)	PDI	% Transmittance	Dispersibilty test (Grade)	Dispersibility test result
F1	273.7	0.342	97.18	A	Pass
F2	250.6	0.449	98.43	A	Pass
F3	203.4	0.413	98.26	A	Pass
F4	389.6	0.384	94.80	A	Pass
F5	428.8	0.458	95.33	A	Pass
F6	196.1	0.123	98.95	A	Pass
F7	264.9	0.429	97.37	A	Pass
F8	384.0	0.529	92.55	B	Pass
F9	509.0	0.780	90.07	B	Pass
F10	443.0	0.480	94.70	B	Pass
F11	307.4	0.450	93.33	C	Fail
F12	640.3	0.789	91.80	C	Fail

Table 4: Self emulsification time and dilution study of L-SNEDDS

Formula	Self emulsification time (sec)	Dilution study in water		Dilution study in 0.1N HCl	
		Drug precipitation	Phase separation	Drug precipitation	Phase separation
F1	49	No	No	No	No
F2	41	No	No	No	No
F3	46	No	No	No	No
F4	50	No	No	No	No
F5	58	No	No	No	No
F6	43	No	No	No	No
F7	48	No	No	No	No
F8	83	No	No	Yes	No
F9	85	No	Yes	No	Yes
F10	92	No	Yes	No	No
F11	129	No	Yes	No	Yes
F12	132	Yes	Yes	Yes	Yes

Table 5: Micromeritic properties of the powder

Bulk density (g/ml)	Tapped density (g/ml)	Hausner's ratio	Carr's index (%)	Angle of repose (θ)
0.24	0.275	1.12	11.1	31.06

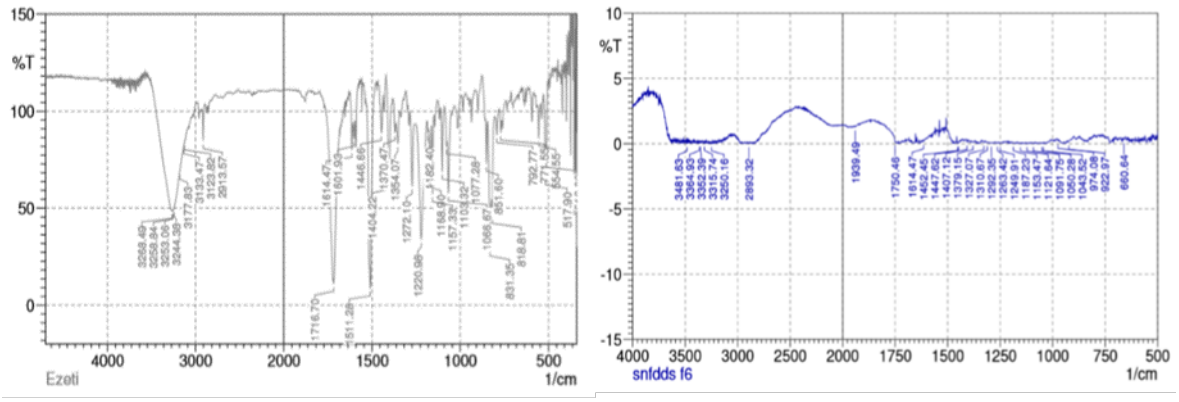

Figure 4: (a) FT-IR data for Ezetimibe; (b) FT-IR data for physical mixture

required for the formation of oil in water emulsion is 8-18.

The surfactants with HLB value more than 10 showed good emulsification. NIS are preferred for oral administration as they can form a stable emulsion. NIS are least affected by changes in pH and ionic strength and are less toxic. The surfactant tween 80 with HLB value 15 showed more drug solubility (140 mg/ml) and emulsification efficiency.

The drug was found to be freely soluble in PEG 400 (152 mg/ml) which had an HLB value of 11.4 and showed good emulsification ability. Tween 80 and PEG 400 had maximum emulsification efficiency with cinnamon oil and was chosen as the surfactant and co-surfactant respectively. The % transmittance of the mixtures is shown in Table 2.

Pseudo ternary phase diagram

Self emulsification region was determined by the Pseudo ternary phase diagram. Phase diagrams says the relationship among the components of the emulsion and their phase behaviour. Surfactant and co-surfactant with different ratios were mixed

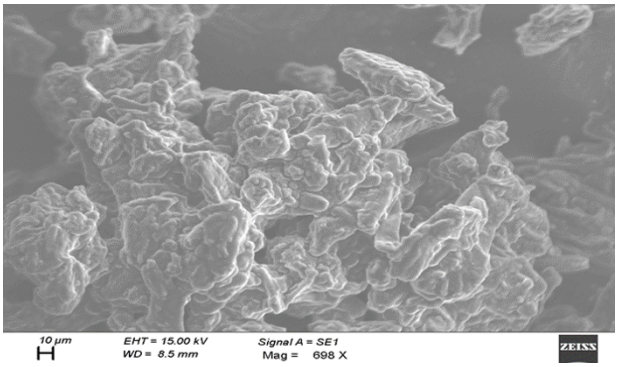

Figure 5: SEM Image for the F6 formulation

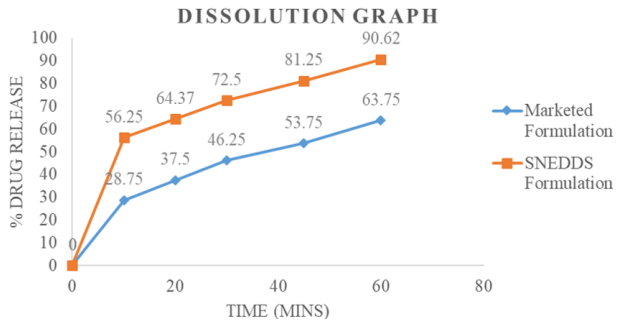

Figure 6: *In-vitro* dissolution data for F6 SNEDDS formulation and marketed formulation

with the oil in increasing concentration of 5%. The nanoemulsion area shows the emulsification ability of the formulations. It is represented in the Figure 2.

Formulation of liquid-SNEDDS

Formulations with different ratios of excipients were prepared according to the procedure. The amount of drug was kept constant for all the formulations.

Characterization of L-SNEDDS

Particle size and PDI

The particle size or globule size of the formulations holds an important role in the stability of the nanoemulsion. The formulations with oil concentration of 20-25% showed less particle size when compared to formulations with 30% oil. The Particle size and PDI of the formulations are given in Table 3.

Emulsification time

The formulations which emulsified spontaneously within 1 minute were considered as good formulations. The formulations F1, F2, F3, F6, F7 showed good emulsification time. These formulations spontaneously formed emulsions when incorporated or introduced in aqueous media. Time for self emulsification is shown in Table 4.

Dilution study

The formulations when diluted with water and 0.1 N HCl were observed for precipitation of drug and phase separation. In water, F9-F12 showed phase separation and F12 formulation also showed drug precipitation. In 0.1 HCl, drug precipitation was observed in formulations F8 and F12 and phase separation was observed in F9, F11 and F12. The result of the dilution study is shown in Table 4.

Dispersibility test

The SNEDDS after administration should disperse completely in the GI fluids without any precipitation. The SNEDDS formulation which showed good clarity and dispersed completely were considered as pass (A or B grade). All the formulations from F1- F10 were A and B grade and these formulations passed the test for dispersibility. The grades of the formulations are mentioned in Table 3.

Percentage transmittance

Transmittance was measured to find out the clarity and transparency of the emulsions. The formulations with highest transmittance were considered as good emulsions and is given in table- 4. F1, F2, F3, F6, F7 formulations showed maximum transmittance and found to have more clarity compared to other formulations. The percentage transmittance of the formulations are given in Table 3.

Characterization of the F6 formulation

Based on the above evaluations and comparing the test result, F6 formulation was selected as the best formulation and further studies were carried out for the F6 formulation.

Phase Contrast Microscopy

The morphology of the liquid SNEDDS was examined by PCM. The Figure 3(a) and Figure 3(b) shows that spherical globules have been formed.

Cloud point determination

Temperature is an important factor for the stability of nanoemulsion as changes in the phase behaviour can occur in higher temperatures when using non-ionic surfactants. The formulations which would remain as one phase transparent system and which a cloud point of above 37°C was considered as an ideal formulation. The cloud point of the F6 formulation was found to be 76°C which indicates that it is stable at physiological temperature.

Centrifugation test

The formulation F6 had no signs of precipitation or instabilities. Hence, L-SNEDDS was found to be stable after centrifugation.

Freeze thaw cycle

F6 formulation was kept in -20°C and +25°C for 48 hrs. The formulation showed no signs of phase sep-

aration and was found to be stable in these temperatures.

Formulation and Characterization of S-SNEDDS

FT-IR Studies

The characteristic peak was observed in the IR spectra of the drug [Figure 4(a)] and the physical mixture [Figure 4(b)]. This confirms that the molecule under the study has not undergone any characteristic changes which shows that there were no compatibilities observed within the components used.

Micromeritic properties of powders

The properties of the powder are mentioned in Table 5.

From the values of the micromeritic properties, it was found that the powder shows good flow properties according to the limits.

Drug content

Drug content of Ezetimibe was determined by using UV spectrophotometric method. The drug content of the formulation was found to be 98.5% which falls within the pharmacopoeial (USP) limits of 93.0%–107.0%.

SEM

The morphology of the powder formulation was found out by SEM. The irregular shaped granular particles indicates that the drug was enclosed in the solid powder formulation. Figure 5 shows the SEM image of the F6 solid powder formulation.

***In-vitro* dissolution**

The *in-vitro* dissolution study for the F6 formulation was compared with the marketed formulation. The *in-vitro* dissolution data for the prepared formulation and marketed formulation is represented in Figure 6. The *in-vitro* dissolution data shows that the drug release at the end of 60 mins from marketed formulation was 63.75 % and from the SNEDDS formulation was 90.62 %. The data shows that the dissolution rate of the prepared SNEDDS was increased by 1.42 times than the marketed formulation.

CONCLUSION

In the present study, it was aimed to enhance the dissolution rate of the poorly water soluble drug Ezetimibe by formulating it in a self nano emulsified system. The data obtained from the study concludes that Ezetimibe can be converted into a self nanoemulsifying drug delivery system with the particle size in the nano range. Among the twelve formulations, F6 was chosen as the best formulation according to the results obtained from the evaluation test. F6 formulation showed a size of 196 nm and the PDI was 0.123. The F6 formulation consisted of the 25% Cinnamon oil, 50% tween 80 and 25% PEG 400. *In-vitro* dissolution study of the F6 formulation and Marketed formulation had a drug release of 90.62 % and 63.75% respectively at the end of 60 minutes. By comparing the *in-vitro* dissolution data, the prepared S-SNEDDS formulation shows 1.42 times drug release than the conventional marketed formulation.

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