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Formulation and Characterization of Solid Self-Nanoemulsifying Drug Delivery System of Ornidazole for Enhanced Dissolution

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Abstract-The solubility of ornidazole was determined in oils, surfactants, co-surfactants, mixture of oils and mixture of surfactants. Among the tested oils, ornidazole exhibited significantly higher solubility in lemon oil compared to all other oils. Span 60 and PEG 400 used in ratios of 3:1 (F10-F12) only exhibited nanoemulsion area with shortest emulsification time (less than 1 min). It was observed that with increase in the ratio of the PEG 400, spontaneity of the self-emulsification process got increased. Avicel PH 102 was utilized as the adsorbent carrier for preparation of S-SNEDDS as it is safe and can be effectively used for production of solid SNEDDS. All the formulated S-SNEDDS exhibited drug content of more than 95% adsorbed on the carrier particles. The values of CI% and HR for Avicel PH 102 adsorbed mixtures indicated acceptable flow properties. The in vitro dissolution studies revealed nearly superimposable drug release profiles for S-SNEDDS powders and L-SNEDDS, respectively. All the formulations exhibited quick drug release characteristics and almost complete drug release in 15-20 minutes. In contrast, the pure drug exhibited only a maximum of 41% release in 60 min duration.

Keywords-Self-emulsifying, Ornidazole, solubility, release, dissolution

I. INTRODUCTION

Oral delivery route is the most convenient route for drug administration to achieve desired therapeutic effects and the greatest degree of patient compliance, especially for chronic condition diseases1. The Biopharmaceutics classification system (BCS) is a useful tool for decision-making in formulation development2 and classifies drugs into four categories depending on solubility and permeability3-5. In drug discovery, about 40% of new drug candidates display poor solubility in water, which leads to low bioavailability, erratic absorption, high intra-subject and inter-subject variability and lack of dose proportionality6.

Self-emulsifying drug delivery systems (SEDDS) are isotropic mixtures of oil, surfactant, co-surfactant and drug that rapidly form fine oil-in-water (o/w) emulsions when introduced into aqueous medium under mild agitation. Self-emulsifying drug delivery systems (SEDDS) are emulsion pre-concentrates or anhydrous forms of emulsion. These systems (SEDDS) are ideally isotropic mixtures of drugs, oils and surfactants, sometimes containing co-surfactant or co-solvents7.

Ornidazole (ODZ) chemically known as 1-chloro-3-(2-methyl-5-nitroimidazole-1-yl) propan-2-ol, is a third generation 5 nitroimidazole derivatives that is commonly used in the treatments of infections caused by the bacterial and protozoa8.

Self-emulsifying drug conveyance frameworks (SEDDS) represent a vital tool in improving oral bioavailability of lipophilic medications. Lipophilic medications can be solubilized in SEDDS formulations, empowering them to be administered as a unit dosage form for oral administration9-14.

The overall goal of the present postulation was to improve the dissolvability, dissolution pace, conceivably the intestinal penetrability and bioavailability of lipophilic medications by using self-nanoemulsifying drug delivery systems (SNEDDS) for oral administration. The prime object of the present work was to design and formulate suitable liquid SNEDDS of ornidazole using different combinations of essential oils, surfactant and co-surfactants, with a view to enhancing the solubility of the drug.

II. MATERIAL AND METHODS

2.1 Calibration curve of ornidazole in methanol

A stock solution of ornidazole (100 mg/100 ml) was prepared in methanol. Diluted ornidazole solution (10 mg / 100 ml) in methanol was prepared from the stock solution. Then, serial dilutions were prepared from that diluted solution in methanol to obtain different concentrations ranging from 10 to 50 µg/ml. The absorbance of these serial dilutions was determined spectrophotometrically at λmax 311 nm, using ethanol as a reference. The measured absorbance was plotted against the corresponding concentrations to obtain the standard calibration curve.

2.2 Drug solubility

The solubility of ornidazole in different oils, surfactants and co-surfactants was determined according to the method of Date and Nagarsenker15. In this method, an excess amount of the drug was mixed with fixed amounts of the oil (castor oil, sesame oil, coconut oil, peanut oil, sunflower oil, eucalyptus oil, lemon oil, oleic acid, sunflower oil, Soyabean oil), surfactants (Tween 80, Tween 20, Span 20, Span 60) and cosurfactants (PEG 400, Propylene glycol, ethanol, butanol) and the mixtures were shaken for 48 hours at 25°C to attain equilibrium. The samples were then centrifuged to remove the undissolved drug, filtered through a 0.45 µm membrane filter, and the supernatant was suitably diluted before spectrophotometric analysis at 311 nm using UV-visible spectrophotometer to determine the amount of the drug dissolved in each excipient.

2.3 Surfactant and oil miscibility

The oil and surfactant in the ratio of 1:1 were shaken at 40°C in 3 ml transparent glass vials. The miscibility was monitored optically and considered to be good when the mixture was transparent.

2.4 Screening of surfactants for emulsifying ability

The emulsification ability of different surfactants was evaluated by mixing the surfactant with the selected oily phase in a 1:1 weight ratio. The mixtures were vortex mixed and diluted up to 200 fold dilution. The ease of formation of an emulsion was assessed by observing the number of inversion of the volumetric flask required to obtain a uniform emulsion.

Table 1 Composition for construction of ternary phase diagram (%w/w)

Formulation	Oil	S mix ratio 1:1	S mix ratio 2:1	S mix ratio 3:1
F1	7	3	-	-
F2	6	4	-	-
F3	5	5	-	-
F4	4	6	-	-
F5	3	7	-	-
F6	7	-	3	-
F7	6	-	4	-
F8	5	-	5	-
F9	4	-	6	-
F10	3	-	7	-
F11	7	-	-	3
F12	6	-	-	4
F13	5	-	-	5
F14	4	-	-	6
F15	3	-	-	7

2.5 Construction of ternary phase diagrams

Based on the solubility of ornidazole, lemon oil was chosen as the oil phase. Span 60 was used as the surfactant and PEG 400 was employed as the cosurfactant. Distilled water was used as the aqueous phase for development of these phase

diagrams. The surfactant and co-surfactant (Smix) in were mixed in different weight ratios (1:1, 2:1, 3:1) so that the concentration of surfactant increases with respect to co-surfactant. The oil phase and each Smix were blended thoroughly in 5 different weight ratios (7:3, 6:4, 5:5, 4:6, 3:7) (Table 1). From these each ratio, 0.1 ml of mixtures was transferred to separate glass beakers. To these contents, 100 ml distilled water was added gently agitated using a magnetic bar at 37°C. The resulted emulsions were examined for clarity, phase separation, and coalescence of oil droplets on standing for 2 h.

2.6 Preparation of ornidazole - loaded self-nanoemulsifying formulations (L-SNEDDs)

Ornidazole was added to the optimized blank ternary systems at a drug loading concentration of 5% w/w. Final mixtures were mixed and shaken for 24 hours at 25°C in a shaking water bath to ensure complete solubilization (Table 2).

Table 2 Composition of ternary systems for L-SNEDDs with nanoemulsion

Formulation	Oil % w/w	Surfactant %w/w	Cosurfactant %w/w	Water % w/w	Smix ratio
F10	40	30	10	20	3:1
F11	40	22.5	7.5	30	3:1
F12	40	15	5	40	3:1

2.7 Evaluation of optimized L-SNEDDS formulation for thermodynamic stability studies and cloud point

Stability of the optimized L-SNEDDS formulation was evaluated at different stress conditions such as heating cooling cycles (4°C and 40°C) and freeze thaw cycles (-21°C and +25°C) along with storage at specified temperature for 48 h. In order to carry out centrifugation stress study, 1 mL of the formulation was diluted to 100 mL with distilled water and centrifuged at 10000 g for 20 min and visually observed for any phase separation16. In order to determine cloud point temperature, 10 mL of diluted L-SNEDDS formulation were gradually heated on a water bath and observed for cloudiness using thermometer. The temperature at which cloudiness appeared was denoted as cloud point.

Characterization of L-SNEDDs

1. Measurement of particle size

The particle size and polydispersity index of the L-SNEDDS was obtained using a dynamic light scattering particle size analyzer.

2. Measurement of zeta potential

The zeta potential of selected formulation was determined using Malvern Zetasizer. Samples were properly diluted with deionized water (1:200) and filtered through a 0.45 µm membrane filter before measurement.

2.7 Preparation of solid SNEDDs (S-SNEDDS) of ornidazole by adsorption technique

The solid SNEDDS of ornidazole were prepared by simple mixing of the liquid SNEDDS formulations with Avicel PH 102 as the adsorbent at different adsorbent: liquid formulation ratios (by weight) (Table 3). Mixing was performed in a mortar using a pestle. The resulting granular mass was passed through a 250 µm sieve for uniformity in particle size. The powder samples were stored over anhydrous calcium chloride in a desiccator until further evaluation.

Table 3 Composition of S-SNEDDS

Formulation	Avicel PH 102	F10	F11	F12
SF1	1	0.25	-	-
SF2	1	0.5	-	-
SF3	1	1	-	-
SF4	1	-	0.25	-
SF5	1	-	0.5	-
SF6	1	-	1	-
SF7	1	-	-	0.25
SF8	1	-	-	0.5
SF9	1	-	-	1

Characterization of S-SNEDDs

1. Angle of repose

Angle of repose was determined according to Carr's method. A glass funnel with a pore diameter of 21

mm was used. The funnel was secured with its tip positioned at a fixed height (2 cm, H) above a sheet of paper. The powder was slowly poured through the funnel until the apex of the pile reached the tip of the funnel. The angle of repose was calculated using the formula:

$$2.\tan\theta = H/R$$

Where θ is the angle of repose and R is the radius of the formed pile. Results are expressed as mean, n = 5.

3. Bulk and tapped density

The bulk volume was assessed by pouring 10 g of the corresponding powder in 100 ml measuring cylinder. The tapped volume was measured by tapping the measuring cylinder to compact the powder.

4. Compressibility

The compressibility was calculated from the data of bulk and tapped density, expressed as Carr's compressibility index (CI) and Hausner ratio (HR). The following formulas were used for the calculations:

$$CI = 100x\ (\ (Vbulk - Vtapped)/Vbulk\ )$$

$$HR = Vbulk/Vtapped$$

2.8 Determination of drug content of ornidazole-loaded solid SNEDDS

An accurately weighed amount of the resulting drug-loaded solid SNEDDS formulation was dispersed in a suitable quantity of methanol and shaken thoroughly to ensure release and dissolution of the drug in ethanol. The samples were centrifuged at 3000 rpm for 15 minutes to separate undissolved excipients. The supernatant was filtered through a 0.45 µm membrane filter and the filtrate was assayed spectrophotometrically for the drug at a wavelength of 311 nm. The drug content in each sample was calculated as milligrams of the drug per gram of the product using the following equation: The experiments were repeated in triplicate for each produced batch of powder and then the results were averaged ± standard deviation.

In vitro dissolution study

The in vitro dissolution studies of different ornidazole SNEDDS formulations were carried out in dissolution apparatus II (Paddle method) according to the requirements specified for ornidazole capsules. The dissolution medium composed of 900 ml phosphate buffer pH 7.2 maintained at 37 ± 0.5°C and the rotational speed was adjusted at 50 rpm. Phosphate buffer pH 7.2 was prepared by mixing 50 ml of 0.2M potassium dihydrogen orthophosphate with 35 ml of 0.2M sodium hydroxide and diluting to 200 ml with water. Volumes of these solutions were corrected accordingly to prepare the total volumes required for dissolution studies. An amount of solid SNEDDS formulation equivalent to 25 mg of ornidazole was filled in suitable number of hard gelatin capsules (size 000) and used for dissolution studies. Samples were withdrawn at predetermined time intervals. An equal volume of fresh dissolution medium maintained at the same temperature was added to keep constant volume during dissolution study. The collected samples were filtered through 0.45 µm syringe filter, suitably diluted using methanol and then assayed for the content of ornidazole by UV spectrophotometry at 311 nm.

III. RESULTS AND DISCUSSION

3.1 Standard calibration curve of ornidazole in methanol

The standard calibration curve of ornidazole was constructed in ethanol to obtain different concentrations ranging from 10 to 50 µg/ml, for which the absorbance readings were determined spectrophotometrically at λmax 311 nm (Figure 1). The standard calibration curve was linear over the concentration range studied and obeys Beer-Lambert's law with a correlation coefficient (r2) 0.998. The corresponding regression equation was found to be Y = 0.0177X-0.0058.

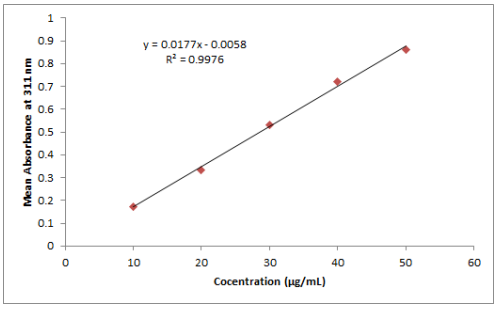

Figure 1 Standard calibration curve of ornidazole in methanol.

3.2 Solubility Studies

The solubility of ornidazole was determined in oils, surfactants, co-surfactants, mixture of oils and mixture of surfactants (Figure 2).

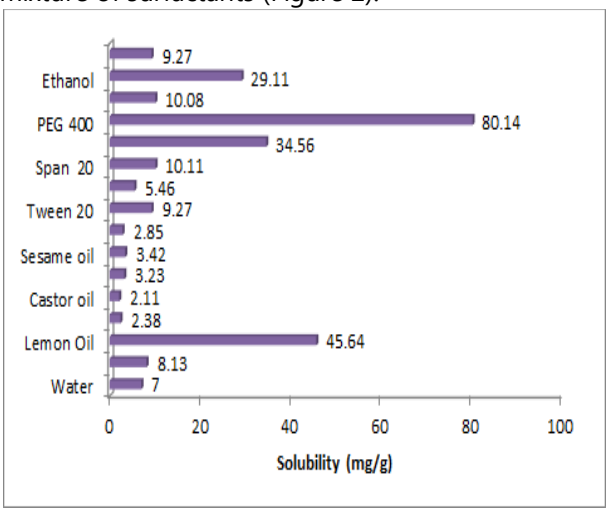

Figure 2 Comparative chart of solubility of ornidazole

Among the tested oils, ornidazole exhibited significantly higher solubility in lemon oil compared to all other oils. In order to form clear nanoemulsion judicious selection of oil, surfactant, co-surfactant and oil to surfactant/co-surfactant ratio is very important. In order to achieve this, it is recommended that a surfactant should have hydrophilic-lipophilic balance (HLB) value more than 10 to form an o/w emulsion. Lemon oil was considered as the oil phase form formulation of the nanoemulsion. The highest solubility was exhibited by Span 60 and it has an HLB value of 4.7 while PEG 400 has HLB value of 13.1.

3.3 Selection of surfactant and cosurfactant

Selection of surfactants should be based on its emulsification efficiency for the selected oil more than its solubilizing potential for the drug17. Therefore, the miscibility of the above surfactants with the selected oil (lemon oil) at a 1:1 weight ratio was investigated according to the method reported by Balakrishnan17 and Date and Nagarsenker16. Emulsification studies showed that Span 60 was able to produce clear nanoemulsion with lemon oil upon dilution, and hence, it was employed as the surfactant in further studies.

Addition of a co-surfactant may provide sufficient flexibility to the interfacial film so that various curvatures can be available to form nanoemulsions over a wide range of composition. Blends of span 60 and PEG 400 were used for the formulation of the nanoemulsions. The appropriate amounts of the selected oil, surfactants and co-surfactant were determined by constructing phase diagrams.

3.4 Construction of ternary phase diagram

In order to identify the self-emulsifying regions and to optimize the percentages of different liquid SNEDDS components, a ternary phase diagram was constructed in the absence of ornidazole (Figure 3).

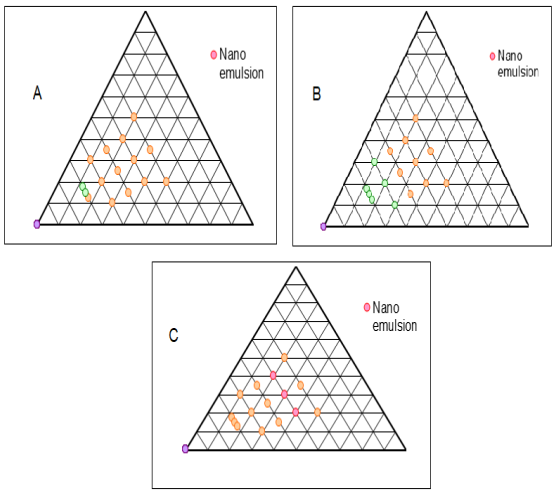

Figure 3 Ternary Phase diagram (A) Smix (1:1)-water-lemon oil (B) Smix (2:1)-water-lemon oil (C) Smix (3:1)-water-lemon oil

The results revealed that only span 60 and PEG 400 used in ratios of 3:1 (F10-F12) led to formation of nanoemulsion area in the shortest emulsification time (less than 1 min). It was observed that with increase in the ratio of the PEG 400, spontaneity of the self-emulsification process got increased. It was observed that higher concentration of surfactant mixture (Smix) resulted in formation of clear transparent emulsions with nanosized droplets. This could be due to higher HLB value of Smix 80 and better solubilization in PEG. The transparent emulsions (F10, F11, & F12) were visually evaluated.

Table 4 Stability and characterization of L-SNEDDS

Formulation	Thermodynamic Stability				Surface characterization		
	Cloud point	Centrifugation	Cooling/Heating	Freeze/Thawing	Mean droplet size	PDI	Zeta potential
F10	89.36	No phase separation	No Phase inversion	No Phase inversion	113.55 ± 6.11	0.913 ± 0.002	-29.1
F11	92.51	No phase separation	No Phase inversion	No Phase inversion	139.48 ± 7.93	0.627 ± 0.005	-25.6
F12	93.04	No phase separation	No Phase inversion	No Phase inversion	181.27 ± 11.56	0.718 ± 0.002	-28.4

for clarity and stability after 48h at room conditions. All tested emulsions remained clear transparent even at the end of 48h. Hence, these ternary phases were selected for ornidaozle loaded SNEDDs.

3.5 Ornidazole loaded self nanoemulsifying formulations (L-SNEDDs)

A fixed ornidazole concentration of 5% w/w was selected to be loaded in all self-emulsifying formulations. It was expected to provide spontaneous emulsification of SNEDDS with a low tendency of drug precipitation upon aqueous dilution. Also, using fixed concentration of ornidazole in all formulations was proposed to exclude the effect of varying the drug concentration on the self-emulsifying efficiency of the systems. It was observed from the results that decreasing the oil content of the formulations resulted in aincrease in the size of formulation droplets.

3.6 Thermodynamic stability and cloud point determination

All the formulations passed the thermodynamic stability studies without any signs of phase separation and precipitation during alternative temperature cycles (4°C and 40°C), freeze thaw cycles (-21°C and +25°C) and centrifugation at 10,000 g indicating good stability of formulations and their emulsions. The cloud point temperature of the tested L-SNEDDS was found to be in the range of 75-97°C (Table 4). Thus, it can be inferred that the developed formulation was stable and do not require a precise storage temperature and it develops a stable emulsion upon administration at physiological temperature in vivo.

3.7 Droplet Size, Polydispersity and zeta potential of L-SNEDDs

The mean droplet size and polydispersity index (PDI) determined for different ornidazole-loaded SNEDDS (F10-12) are shown in Table 4. Incorporation of different amount of Smix into ornidazole-loaded SNEDD formulations resulted in significantly different droplet size. Among the tested formulations, SNEDDS formulations prepared with 3:1 Smix ratio exhibited lower droplet size compared to formulations in which the amount of surfactant was low.

3.8 Solid SNEDDs (S-SNEDDS) of ornidazole

Filling of liquid SNEDDSs into hard or soft gelatin capsules is the simplest way for oral administration of these formulations. Capsule filling is suitable for highly potent drugs and provides high drug loading which is determined by the solubility of the drug as well as the capacity of the capsule. The simplest method to convert liquid SNEDDS formulations into solid ones is by adsorption of the liquid formulation onto the surface of solid carriers that are highly porous and/or possess high specific surface area. Avicel PH 102 was utilized as the adsorbent carrier for preparation of S-SNEDDS as it is safe and can be effectively used for production of solid SNEDDS18.

3.9 Micromeritic properties and drug content

Determination of the flow properties of solid SNEDDS powder formulations helps to identify the most appropriate formulation that can be successfully filled into capsules or alternatively, compressed into tablets. According to the scale of flowability, powder formulations possessing angle of repose in the range of 25°– 35° are considered as having acceptable flow properties although powder formulations that show angle of repose in the range of 40°– 50° may be adequately manufactured. Also, powder formulations having CI% values below 25 are considered to possess good flow properties. In addition, HR values less

than or equal to 1.25 indicate good flow properties although HR values less than 1.34 denote passable flow (Table 5).

Table 5Flow properties of S-SNEDDS

Formulation	Angle of repose (q°)	Bulk density	Tapped density	Carr's Index	Hausner's Ratio	Drug Content
SF1	38.92 ±0.28	0.30 ±0.01	0.33± 0.0	9.09 ±2.73	1.10± 0.03	96.01 ± 1.33
SF2	37.47 ±0.69	0.37 ±0.01	0.41± 0.01	9.76 ±0.00	1.11± 0.00	95.65 ± 1.08
SF3	38.01 ±0.71	0.50 ±0.01	0.54± 0.01	7.41 ±2.73	1.08± 0.03	95.77 ± 1.65
SF4	38.71 ±1.13	0.31 ±0.00	0.34± 0.01	8.82 ±2.89	1.10± 0.03	97.11 ± 3.53
SF5	39.52 ±0.82	0.36 ±0.00	0.40± 0.01	10.00 ±2.89	1.11± 0.03	97.06 ± 1.22
SF6	37.93 ±0.32	0.51 ±0.00	0.54± 0.00	5.56 ±0.00	1.06± 0.00	96.20 ± 1.54
SF7	38.59 ±0.34	0.31 ±0.01	0.34± 0.00	8.82 ±2.73	1.10± 0.03	95.93 ± 3.81
SF8	36.26 ±0.25	0.36 ±0.00	0.39± 0.01	7.69 ±2.89	1.08± 0.03	97.02 ± 1.23
SF9	43.48 ±0.89	0.49 ±0.01	0.52± 0.00	5.77 ±2.89	1.06± 0.03	98.14 ± 1.33

All the formulated S-SNEDDS exhibited drug content of more than 95% adsorbed on the carrier particles. The values of CI% and HR for Avicel PH 102 adsorbed mixtures indicated acceptable flow properties. These free flowing solid SNEDDS formulations of ornidazole prepared with higher amounts of liquid SNEDDS formulations will consequently contain higher amounts of the drug and therefore, an amount equivalent to the pharmacological dose of the drug can be weighed from theses formulations and filled into capsules for additional analysis. SF1, SF4 & SF9 (with highest drug contents in each L-SNEDDS batch) was studied for drug release.

1. In vitro dissolution study

The in vitro dissolution studies revealed nearly superimposable drug release profiles for S-SNEDDS powders vis-à-vis the L-SNEDDS, respectively. All the formulations exhibited quick drug release characteristics and almost complete drug release in 15-20 minutes (Figure 4). In contrast, the pure drug exhibited only a maximum of 41 % release in 60 min duration.

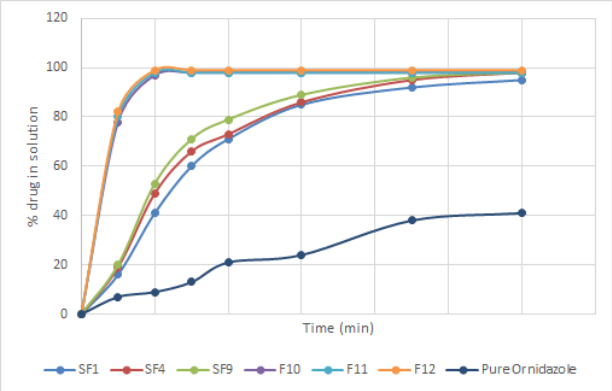

Figure 4 In vitro dissolution profile of S-SNEDDS, L-SNEDDS and ornidazole

Ornidazole-loaded liquid SNEDDS formulations (F1, F4, F9) exhibited optimal dissolution performance when compared to other formulations. High dissolution profiles of liquid SNEDDS are due to quick formation of o/w nanoemulsions with small droplet size upon exposure to dissolution medium with gentle agitation. In addition, the presence of the drug in a dissolved state in liquid SNEDDS formulations avoids the dissolution rate-limiting

step required for crystalline drugs. On the other hand, the dissolution of ornidazole from different solid SNEDDS formulations was intermediate between the maximum dissolution shown by liquid SNEDDS formulations and the minimum dissolution exhibited by pure drug powder.

V. CONCLUSION

The bioavailability of the lipophilic drugs can be enhanced by formulating them as SNEDDS. The present study ratifies the fact that adsorption of liquid SNEDDS on to the surface of solid adsorbent can be a useful approach to incorporate large amount of drugs into the formulation and the release behavior witnessed from the present investigation proves that the bioavailability of the lipophilic drug (ornidazole) could be almost doubled by formulating it as SNEDDS.

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