Original Article

Application Of Self Nano Emulsifying Drug Delivery System For Clarithromycin

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Abstract

The primary goal of this thesis is to develop a novel Self Nano-emulsifying drug delivery system to improve drug bioavailability in vitro and to increase clinical efficacy when administered orally.

Keywords: - Self nano-emulsifying drug delivery system, Clarithromycin, Pseudo ternary phase diagram, Bioavailability

INTRODUCTION

SNEDDS stands for the distribution of isotropic arrangements containing oil, co-surfactants, and surfactants. In SNEDDS, some globules are globules that are sustained as series of smaller than 100 nm under distribution in water dispersion. Drugs that are poorly soluble in water have recently had their solubility improved by SNEDDS and SEDDS. The natural performance that NE has expressed appears to be either clear or glassy. As it was constructed in small drop size, it was kinetically steady as opposed to sedimentation and caking over a long period. The use of Nano-emulsion in the formulation of oral dosages encouraged results by enhancing the drug's efficacy in areas where it could increase bioavailability, permeability, and therapeutic effects. Apart from the ability of self-emulsifying preparations to affect quite a few elements of HLB-Value with surfactant-concentration, the manufacturing of self-emulsifying preparations includes various combinations in surfactant and oil mixtures.

Clarithromycin belong to the macrolide class of antibiotics. It has a half life of 3-4 hours and a half-life of 5-7 hours. Clarithromycin has an absolute bioavailability of about 50%. Clarithromycin is a BCS class I antibiotic. As a result, the primary goal of the study is to create and test liquid and solid SNEDDS containing clarithromycin to order to improve its oral bioavailability by increasing drug solubility. We attempted to improve dissolution rate of clarithromycin in this study to order to increase its effectiveness and minimize variability.

MATERIALS AND METHODS

Materials:

S. No.	Materials	Company
1.	Clarithromycin	Madras Pharmaceuticals pvt Ltd
2.	Groundnut oil	Local Market
3.	Ethanol	SISCO Scientific pvt. Ltd
4.	Tween 80	SISCO Scientific pvt. Ltd
5.	Aerosil 200	SISCO Scientific pvt. Ltd

Instrumentation:

Equipment's	Manufacturer
UV-visible Spectro photo meter	Shimadzu
Dissolution apparatus	Lab India USP-8000
FT_IR spectrophotometer	Thermo electron corporation IR-200
Scanning Electron Microscopy	Hitachi S-3000N
Transmission Electron Microscopy	
Zeta sizer	Horiba Scientific SZ-100

Methods:

Produce of Self-micro emulsion:

Phase Titration Method: With the assistant of a phase diagram microemulsion is ready by the continual emulsification method. When we mixed various ingredients, some interactions may occur with the assistance of the phase diagram we are able to predict it. Looking on the concentration and chemical composition microemulsion is made with different structures like (various gels, oil dispersion, emulsion, micelles, lamellar, hexagonal, and cubic). There are two method to search out the interactions between the ingredients quaternary phase diagram and pseudo ternary phase diagram. It takes a lot of time and effort to process this quaternary phase diagram. Pseudo ternary phase diagram is most convenient method to seek out the zone of microemulsion.

Phase inversion method: With response to temperature or by adding more amount of dispersion introduce in microemulsion phase inversion is occurs. The in vitro and in vivo release of drug is tormented by physical changes like change in particle size because of drastically physical changes occurred. In non- ionic surfactant by changing temperature phase inversion is occur (w/o microemulsion at higher temperature and o/w micro emulsion in low temperature) this method is named phase inversion temperature method. Rather than temperature alone another parameters like pH or salt concentration could also be considered. By changing the fraction of water volume with transition time spontaneous radius of curvature may be obtained.

Solidification techniques for converting liquid SNEDDS to solid-SNEDDS:

Spray drying: In this method after preparing nano-emulsion it should be sprayed into spray dryer, when the droplets entered into drying chamber solvent present in the emulsion is evaporate and leaving a fine dry particle under controlled air flow and temperature. This particle can be collected and filled in hard gelatin capsule or compressed in to tablets.

Adsorption of solid carriers: The adsorption technique is simple and most common method, In this technique liquid micro emulsion is added to the suitable solid carrier and simultaneously mixing by the help of mixer or blender, dry powder is formed then it is filled in to capsule or made as a tablet before punching as a tablet the excipients are added to it. Up to 70% of solid carriers can be absorbed by liquid emulsion. The main advantage of this method is drug content uniformity.

Melt granulation: In this method the binder is melted at low temperature and it gives dry granules. It is a single step procedure. This method has more advantage than wet granulation method. There is no needed of adding solvent. The liquid addition and further drying process is skipped by this method. Most of the semisolid and solid lipids are melt able binders. The mixing time, impeller speed, viscosity of the binder and binder particle size are the parameters which can affect the granulation process.

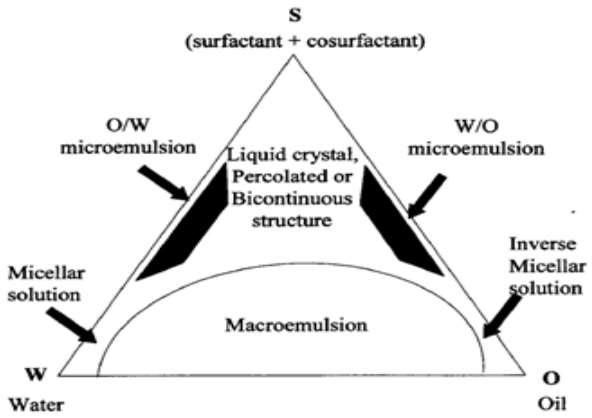
Construction of ternary phase diagrams

The ternary pseudo phase diagram was divided into two regions: biphasic emulsion region and monophasic microemulsion region. In a pseudo-ternary phase diagram study, systems consisting of surfactant, oil and co-surfactants need to be titrated against water and self-emulsification event was selected at infinite dilution.

By using the water titration method pseudo ternary phase diagrams were created. At room temperature, double demineralized water was introduced drop by drop to the combination of surfactant and oil combination segment.

The ternary phase study was conducted with selected oils as oil phases, surfactants and co surfactants from solubility studies. The ratios of surfactant: co surfactant were taken as 1:1, 1:2, 2:1 and 2:3. Titration was forwarded by drop wise addition of water to oil phase and surfactant blend with a varying ratio of oil to surfactant mix ranging from 9:1 to 1:9. After addition of water, the mixture was gently stirred in a beaker for 2-3 minutes with a glass rod or magnetic stirrer until homogeneous solution has been obtained. With every addition, the device became more well-known for its appearance. The titration's give-up factor was recorded as the point at which the solution became turbid. The amount of aqueous segment required to produce the aggregate turbidity was recorded.

Several endpoints were identified as critical points between regions in each of the titration runs. The critical point was the specific composition at which the appearance (haze) of the mixture changed significantly.



Water titration method

From the ternary plots, the composition of oil and S_{mix} which can form microemulsion in presence of drug were taken and the same composition was considered for the preparation.

Clarithromycin was continuously stirred into the oily phase while being added in small increments. The chosen surfactant and co-surfactant were combined in the surfactant system separately according to their predetermined ratios. An oil phase containing drugs was added to the surfactant system solution while it was continuously stirred and vortexed. Stirring was kept up until a homogeneous mixture was achieved. For the ensuing evaluations, the mixture was then maintained at 25°C.

Excipients compatibility: Infrared (IR) spectroscopy studies of drug and drug in the formulation were recorded in FTIR spectrophotometer (Thermo-IR 200) using a sandwich method with Potassium bromide as a blank and a background spectrum collected under similar circumstances. Each spectrum was created using scans with a spectral resolution of 2 cm-1 that were collected in the range of 4000 - 400 cm-1.

Standard curve of clarithromycin with ethanol: A 0.1g of clarithromycin was dissolved in 100 mililiter of methanol and further dilution were made using buffer to get concentrations ranging from 10,20,30,40 and 50 µg/ml. The transmission density of solution was measured at 210 nm using UV visible spectrophotometer.

Solubility Studies: Clarithromycin solubility in various oils, surfactants, and cosurfactants was determined using the shaker method. Each vehicle received an excess of valsartan, which was then vortexed for 30 seconds. In a thermostatically controlled shaker, the mixture was jolted for 1 hour. The mixture was then filtered through a 0.40 m Millipore membrane filter. The drug concentration was determined using a UV validated method at 210 nm with samples suitably diluted with ethanol as a blank. The experiment was carried out three times.

LIMITATIONS OF SNEDDS:

1. GIT irritation increases as the amount of surfactant in self-emulsifying formulations (30-60%) increases.
2. Furthermore, it is known that volatile co-solvents in conventional self-emulsifying formulations migrate into the shells of hard or soft gelatin capsules, resulting in the precipitation of the hydrophobic drug.
3. Chemical instabilities of drug and high surfactant concentrations.

Advantages of SNEDDS:

1. Increase oral bioavailability in minimum dose,
2. Drug(s) are targeted at a specific absorption window in the Gastrointestinal tract.
3. Prevent drug degradation due to the unfavorable environment in the gut.
4. Delivery profiles was control.
5. Minimize variability including effects of food.
6. Sensitive drug substance prevention.
7. More payloads of drugs.
8. Dosage forms can be solid or liquid.

SNEDDS disadvantages:

1. It is difficult to predict in vitro models for formulation evaluation.
2. More amount of surfactant concentration used in this formulation which irritates GIT.
3. Migration of a volatile co-solvent into either the soft or hard gelatin capsule's outer shell.
4. The precipitation potential of drug on dilution may be increased due to the dilution effect of lypophobic solvent.
5. Several components present in the formulations become more challenging to validate.

Factors affecting SNEDDS:

Mainly five factors which affects the SNEDDS formulation such as solubility of drug in lipid phase, charge of emulsion droplets, equilibrium solubility, drug dose, polarity of lipid phase.

a. **Drug solubility in the lipid phase:** In SNEDDS formulations the drug in solution state can be retained by oil solubility of the drug. The solvent capacity of surfactant and co-surfactant in SNEDDS can be decreased by solubilization of drug in surfactant and co-surfactant which leads to precipitation.

b. **Equilibrium solubility:** This could be due to the possibility of precipitation in the gut. This formulation can take up to five days to obtain equilibrium, and after the emulsification events, the drug can maintain its supersaturated state for up to 24 hours.

c. **Charge on emulsion droplets:** Most of the biological studies proved that the absorption cells and also other cells inside the human body have negative charges when co-related to mucosal solution present in the lumen. Add oleyl amine to emulsion droplets to produce positively charged particles. The SMEDDS react with calcium carbonate-2 monolayer and the rat's intestine (mucosal surface). In young rats the oral bio availability of progesterone is improved by this formulation. Because of the production of the positively charged emulsion, benzoic acid has dual capabilities in self-emulsifying drug delivery systems. It can boost the self-micro-emulsifying oil formulations and self-emulsifying oily formulations in 0.1 normality hydrochloric acid.

d. **The linear polarization of the oil phase:** The active ingredient released from micro emulsion is depends on the linear polarization of the oil phase. Molecular weight of lipophilic part, length of HLB chain, fatty acid unsaturation and concentration of the emulsifier are the agents for the polarity of droplets. The fast rate of drug release in to the aqueous phase is due to high polarity. The formulation which have highest polarity and oil phase will give high release rate.

e. **Drug dose:** In general, high dose of drug is not suitable for SNEDDS formulation. Even though such drug can more soluble in any one of the oils used in formulation. The drug having log P value of 2 and it cannot soluble in oil and water are not suitable for SNEDDS formulation.

Applications:

1. **Improved in oral bioavailability:** The potential of SNEDDS to give the drug in a soluble and nano- emulsified form of GIT (particle length ranging from one to one hundred nm) and subsequent growth in precise floor neighborhood allow for large green drug delivery through to the absorbent brush border membrane and the aqueous intestinal boundary layer, resulting in a high bioavailability. E.g. the evaluation of the pill formulation for halofantrine mentioned an increase in drug bioavailability that was roughly 6–8 times greater.

2. **Ease of manufacture and scale-up:** For large-scale production, the ease of manufacture and scale-up of SNEDDS necessitates quite simple and cost-effective production centers such as simple mixers with agitators and volumetric liquid filling devices. The above explains the hobby enterprise withinside the SNEDDS.

3. **Reduced inter- and intra-concern variations, as well as meal effects:** Due to patient non-compliance and the fact that some tablets have significant inter- and intra-subject variation in absorption, the drug's overall effectiveness is decreased. Food has become the primary component influencing the drug's healing overall performance within the body. Such tablets had benefited from SNEDDS changed into unbiased meals and SNEDDS provides reproducibility of plasma profile.

4. **The capacity to provide peptides susceptible to enzyme hydrolysis in GIT:** SNEDDS outperformed other drug transport structures due to its ability to supply macromolecules as well as inhibitors, enzyme substrates, hormones and peptides, as well as its ability to protect against enzymatic hydrolysis. If the polysorbate were an emulsifier in the nanoemulsion formulation, intestinal hydrolysis of prodrugs via cholinesterase could be covered. These structures are suitable for heat-labile drugs and peptides because they form spontaneously and without the use of energy or heating.

5. **No affect on of lipid digestion process:** The overall performance of SNEDDS was no longer supported by fat oxidation, emulsification by bile acids, mixed micelle formation and movement of pancreatic lipases, in contrast to lipid-based drug delivery systems.

6. **Increased drug loading capacity:** In herbal lipids, the solubility of badly water-soluble tablets with such an intermediate partition coefficient was commonly low, but much higher in co-surfactants, amhiphilic surfactants, and co-solvents.

S-SNEDDS formulation components

1. API

2. Oil phase
3. Surface active agent
4. Co-surfactant
5. Co-solvents
6. Polymers

OILS

The oil phase is critical in the formulation of SNEDDS. It is primarily related to O/W nanoemulsion because physicochemical properties of oil such as viscosity, polarity, and molecular volume significantly govern the spontaneity of the nanoemulsification process, biological fate of Nanoemulsions, drug solubility, and the droplet size of the Nanoemulsion. The oil is critical to maximizing the solubility of preferred drug candidates and for selecting the oily phase for Nanoemulsion formulation. With its high drug-loading ability, this is frequently the most important approach. Triglycerides found in long-chain fatty acids help to reduce unsaturation and prevent oxidative degradation. The size of the nanoemulsion is proportional to the lipid solubility of the oil and the density of the oily phase in SNEDDS. Investigations by Anton, Vandamme, and Sadurni back up the previously said statement. Long-chain triglycerides have been proven to have a higher ability to promote the lymphatic transport of drugs (responsible for preventing first-pass metabolism of drugs), whereas moderate-chain mono- and di-glycerides have higher solubility capacity for lipophilic drugs and permeation-enhancing properties. As a result, a single oily component will struggle to have optimal properties for drug delivery and nano-emulsification. In some cases, a mix of oils may be utilized to achieve the best oily phase properties. An analogous idea has been used for microemulsions and nanoemulsions. In some cases, medium-chain triglyceride and a mixture of fixed oil is used to achieve a optimal balance of emulsification and drug loading. Since edible oils cannot solubilize drugs with higher concentrations, they are not used in the SNEDDS formulation. Hydrolyzed vegetable oils are used as a result of the development of better emulsifying process with much more emulsifiers suitable for oral administration. They advocate for formulation and physiological compensation. The oils in SNEDDS are being replaced by moderate-chain semi-synthetic chemicals known as amphiphilic compounds with surfactant properties.

SURFACTANTS

Surfactants are ions and molecules that are adsorb just at the matrix. It is capable of preventing interfacial tension and providing interfacial area. The choice of surfactant is also critical in the composition of SNEDDS. Surfactant properties like hydrophilic-lipophilic balance (in oil), viscosity, cloud point and affinity for the lipid phase all have an impact on the nano emulsification process, self-nano emulsification area, and thus droplet size of nanoemulsion. The concentration of surfactant in the SNEDDS has a significant impact on the droplet size of nanoemulsions. During surfactant selection, the evaluation of the preselected surfactant for the ideal way of administration, as well as its regulatory status, must be considered.

Surfactants are mainly divided into 4 groups-

- Cationic surfactants
- Anionic surfactants
- Ampholytic surfactants
- Non-ionic surfactants

Cationic surfactants

An ionic surfactant's hydrophilic group or head carries a net charge. If the charge is positive, the surfactant is known as a cationic surfactant. Primary, secondary, tertiary, and quaternary ammonium salts of higher alkyl groups, such as octadecyl trimethyl ammonium chloride and C12-14 alkyldimethylbenzyl ammonium chloride, are the most common cationic surfactants.

Anionic surfactants

An ionic surfactant's hydrophilic group or head carries a net charge. When the charge is negative, the surfactant is referred to as an anionic surfactant. Anionic surfactants include sodium lauryl sulphate, sodium lauryl polyoxyethylene ether sulphate, sodium cetyl polyoxyethylene ether phosphate, soybean phospholipids (lecithin), carboxyl (RCOO-), sulphonate (RSO3 -), or sulphate (ROSO3-). Sodium lauryl sulphate, potassium laurate.

Ampholytic surfactants

Surfactant units contain both positive and negative charges, such as Sulfobetaines.

Non-ionic surfactants

The hydrophilic group has no charge, but it can contain strong polar functional groups such as hydroxyl or polyoxyethylene, allowing it to be water soluble (OCH2CH2O). Polysorbates and sorbitan esters (Spans) are two examples (Tween 20).

Non-ionic surfactant molecules are more stable than ionic surfactant molecules, and they are nontoxic and thermodynamically stable molecules with a high hydrophilic-lipophilic balance (HLB) to produce stable SNEDDS. To create stable SNEDDS, surfactant concentrations of 30-60% are used. The formation of SNEDDS is caused by higher surfactant, co-surfactant, and oil ratios in lipid mixtures of molecules, and it is responsible for increasing the oral bioavailability of poorly water-soluble drugs.

CO SURFACTANTS

It performs a similar function to the surfactant unit. Co-surfactant was added alongside a surfactant unit or a combination of surfactant units to increase the surfactant's ability to improve the water solubility of a poorly water-soluble drug. The most important role of co-surfactant in SNEDDS is to reduce the oil-water interface, increase surface area, and allow for the spontaneous formation of nanoemulsion. Higher surfactant concentrations (> 30% w/w) are required for SNEDDS formulations, which can be condensed with the addition of a co-surfactant. These, when combined with surfactants, reduce interfacial tension to a -ve value, at which point it expands to form fine droplets that are then adsorbed with higher amounts of surfactant and surfactant/co-surfactant until the interfacial tension returns to a +ve value. This is known as "spontaneous emulsification." Many non-ionic surfactants do not require the addition of co-surfactants to SNEDDS. Co-surfactants with HLB values ranging from 10 to 14 are used in SNEDDS. Alcohols with medium chain lengths, such as hexanol, pentanol, and octanol, are hydrophilic co-surfactants that reduce the interface between oil and water, allowing for impulsive microemulsion formation.

CO-SOLVENTS

A high concentration of surfactant is usually required for an effective self-emulsifying formulation. As a result, co-solvents such as ethanol, propylene glycol, and polyethylene glycol are needed to aid in the dissolution of large amounts of hydrophilic surfactant. In the microemulsion system, these co-solvents can also act as co-surfactants. Alcohol and other volatile co-solvents, on the other hand, have the disadvantage of evaporating into the shell of soft or hard gelatin capsules, resulting in drug precipitation.

POLYMERS

We use an inert polymer matrix that is non-ionizable at physiological pH and can form a matrix. Surfactants include hydroxyl propyl methyl cellulose and ethyl cellulose.

EVALUATION:

1. **Droplet Size Determination:** The droplet size of emulsion was determined by using Photon Correlation Spectroscopy (PCS) or Laser Diffraction Techniques or Dynamic Light Scattering (DLS). The particle size was measured by using various equipment's such as zeta sizer, Particle size analyser and master sizer. The particle size of 10-5000nm are able to measure by this equipment's.

2. **Viscosity measurement:** Using a Brookfield viscometer and spindle no. 63 at 45, 75, and 120 rpm for 5 minutes at 25 °C, the viscosity of the optimized microemulsion was measured.

3. **Percentage content of drugs:** The drug content of the microemulsion formulation was determined by transferring 1 ml sample of the formulation into a volumetric flask and volume was adjusted to 100 ml using ethanol. After equilibration and suitable dilutions, the absorbance of the sample was determined using the UV spectrophotometer at 210 nm.

4. **Determination of pH:** Using a glass electrode and a pH meter at room temperature, the pH values of the optimized samples were determined.

5. **Zeta potential measurement:** Zeta potential for microemulsion was determined using zeta sizer. Samples were placed in clear disposable zeta cells and results were record.

6. **Differential Scanning Calorimetry (DSC):** DSC 60 was utilised to find out the Differential Scanning Calorimetry for SNEDDS. Solid and liquid sample should be applied over the aluminium pan and record the result. If there are any chemical interactions such as crystallisation, thermal behaviour of excipients melting, solid to solid transition temperature.

7. **Fourier Transform-Infrared Spectroscopy:** By using FT_IR (Fourier transform- infrared) for SNEDDS formulations can be examined. Liquid is placed in sample cell and record the result. If there is any chemical interactions it should be determined by using FT_IR.

8. **Visual Examination:** To determine self-emulsification property (60 mg) of formulation was mixed with 100 ml of water in a flask at 25 degree centigrade and stirred well. If there is transparent emulsion produced it was good formulation otherwise it should be poor formulation. It is necessary to construct the phase diagram to find out the good formulation.

9. **Invitro Release:** The percentage amount of dug release at particular time was determined by USP dissolution apparatus and UV-Spectrophotometer. The test was performed in 900ml basket containing dissolution media (purified distilled water). SNEDDS was placed inside the dialysis bag and place inside the dissolution media under controlled temperature and paddle rotation. At particular interval of time 10ml of sample was withdrawn and replaced with equal amount of fresh dissolution media immediately. Withdrawn sample was filtered and dilute with suitable solvent and analysed spectrophotometrically, and determined the percentage drug release by using Beer lambert's law.

10. **Determination of Self Emulsification Time:** The time taken to produce self- emulsion is called emulsification time. It can be determined by using dissolution apparatus (USP 2). In 500 ml of purified water 300 mg of each SNEDDS formulation was added at 37 degree centigrade with agitation by rotating paddle at 50 rpm and find out the emulsification time visually.

11. **In vitro dissolution study:** In vitro, drug release studies from liquid microemulsion were carried out by using a USP type I dissolution apparatus with 50 rpm. The dissolution medium consists of 900 ml of phosphate buffer of pH6.8 maintained at 37± 0.5ºC. About 5 ml of liquid microemulsion equivalent to 50mg of clarithromycin was filled in a dialysis tube and added to the dissolution medium. At pre-decided time intervals, a five ml of aliquot was turned into the withdrawn and an equal extent of clean dissolution medium was turned into at once added. The amount of drug launched turned into anticipated with the aid of using measuring absorbance at 210 nm with the usage of a UV visible spectrophotometer.

12. **TEM Analysis:** The surface morphology of SNEDDS was characterized by Transmission Electron Microscopy. Samples were diluted with double distilled water and stained and well dried on the surface of grid and placed under observation.

13. **Scanning electron microscopy (SEM) Analysis:** Surface morphology of the S-SNEDDS was investigated by SEM, operating at 50 kV (SU1510).

14. **Zeta-potential:** Zeta-potential calculated as rate of NE exterior plane drop. Preparations (0.1ml) were watery with hundred era by fold Dis.tld dampen & examined by means of Zetasizer.

15. **Examination of Stability:** Stability is determining a formulation tolerance. The purity, as well as quality in SNEDDS determination, is a major part of stability examination. SNEDDS preparations were analyzed because of NE steady which on undergoing the machine-like strain state of affairs (centrifugation: 2000-4000rpm) with favorable preparations stored at unusual temp. Starts as *4 ± 1°C40 ± 1°C* unique time-intervals. Look as machine-like strain circumstances as a Physio-chemical steady nature of SNEDDS were experimentally formative % point split, contravention of SNEDDS by meaning filled differing. Studies holds not pertinent modification in the preparations then 1hour timed centrifugation: two thousand revolution per minute.

16. **Filter-paper test:** Experiment relay the piece of information in which Oilin-Water SNEDDS was applying results briskly as droplets in filter-paper. Another side, Water-in-oil SNEDDS was migrating barely slowly. This sense was not second-hand for decidedly tacky creams.

17. **In vitro dispersion study:** Efficacy in self-emulsification of Nano mixture (oralmixture) were single-minded via customary USP-XXII closure-equipment-2. 1ml of both preparation is new to half a litre (500ml) dampen on *36 ± 0.5ºC*. (Propeler rotating at fifty rotation per min providing mild agitation).

CONCLUSION

The results of present study suggest that formulating clarithromycin as nano-emulsion, could improve its intestinal permeability in comparision with the pure drug solution. S-SNEDDS have been exhibited smooth and uniform surfaces and thereby it was inferred that the proper adsorption of Aerosil onto the carrier.

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