

FORMULATION AND EVALUATION OF NOVEL LIPID BASED SOLID SELF NANO EMULSIFYING DRUG DELIVERY SYSTEM OF REPAGLINIDE

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ABSTRACT

Objective: Aim of present study was to develop solid self nano emulsifying drug delivery system (S-SNEDDS) with Neusillin US2 for enhancement of dissolution rate of model drug Repaglinide.

Methods: SNEDDS were prepared using Olive oil, Miglyol, Cremophore RH 40, Capryol 90 and Labrasol. For formulation of stable SNEDDS, nano emulsion region was identified by constructing pseudo ternary phase diagram containing different proportion of surfactant, co-surfactant, oil and water. The self emulsification properties, % transmittance, droplet size, and zeta potential of these formulations were studied upon dilution with water. S-SNEDDS was prepared by adsorption technique using Neusillin US2 as solid carrier. Prepared S-SNEDDS was evaluated for flow properties, drug content, FT-IR and in-vitro dissolution study.

Results: Showed that prepared liquid SNEDDS passed all evaluation tests. Dilution study by visual observation showed that there was spontaneous micro emulsification and no sign of phase separation. Droplet size was found to be below 10 nm. S-SNEDDS showed good flow property and drug content. Dissolution profile of S-SNEDDS was significantly higher than plain drug.

Conclusion: Thus our studies conformed that SNEDDS can be used as a possible alternative to conventional oral formulation of Repaglinide.

Keywords: Repaglinide, S-SNEDDS, Droplet size, Zeta potential, *In vitro* dissolution and drug content.

INTRODUCTION

Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules. Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown. Currently only 8% of new drug candidates have both high solubility and permeability¹. Various approaches should use to improve the dissolution rate of the drug. Among them, Self nano emulsifying drug delivery systems (SNEDDS) have shown great pledge for enhancing bioavailability of poorly soluble compounds^{2,3}. SNEDDS^{4,5,6,7} are isotropic and thermodynamically stable solutions consisting of an oil⁸, surfactant, co-surfactant and drug mixtures that spontaneously forms oil in- water nano emulsions⁹ when mixed with water under gentle stirring. The basic principle of this system is its ability to form fine oil-in-water (o/w) nano emulsion under gentle agitation following dilution by aqueous phases. This spontaneous formation of an emulsion in the GI tract presents the drug in a solubilized form, and the small size of the formed droplet provides a large interfacial surface area for drug absorption. Particularly for BCS class II substances, the bioavailability may be enhanced by increasing the solubility and dissolution rate of the drug in the gastro-intestinal fluids. SNEDDS are generally encapsulated either in hard or soft gelatin capsules. SNEDDS may interact with the capsule resulting in either brittleness or softness of the shell¹⁰. To overcome this problem SNEDDS need to convert into Solid SNEDDS. Many techniques are offered to convert conventional liquid SNEDDS to solid such as adsorption to solid carriers, spray drying, spray cooling, melt granulation, rotary evaporation, freeze drying and high pressure homogenization^{11,12,13,14}. But adsorption process is simple and involves simply addition of the liquid formulation to solid carriers by mixing in a blender. The resulting powder may then be filled directly into capsules or mixed with suitable excipients before compression into tablets.

Repaglinide is an anti-diabetic drug. Repaglinide lowers blood glucose by stimulating the release of insulin from the pancreas. It

achieves this by closing ATP-dependent potassium channels in the membrane of the beta cells. This depolarizes the beta cells, opening the cells calcium channels, and the resulting calcium influx induces insulin secretion. Repaglinide belongs to class II drug in BCS classification. The solubility of Repaglinide in aqueous medium is very low. The half life of Repaglinide is 1 hour which is very low. This results into poor bioavailability after oral administration. Hence it is necessary to enhance aqueous solubility and dissolution rate of Repaglinide. The main objective of the study was to formulate, develop and evaluate an optimal S-SNEDDS formulation containing Repaglinide by adsorption technique using Neusillin US2 as solid carrier.

MATERIALS AND METHODS

Repaglinide was obtained from Mylan Laboratory, Hyderabad. Miglyol, Cremophore RH 40, Capryol 90, Transcutol 90 and Labrasol were gift from Gattefosse, Mumbai, India. All other chemicals were reagent grade.

Characterization of Liquid SNEDDS

Solubility studies:

1gm of each selected oil, surfactant, co-surfactant and co-solvent was added in glass vial. Excess amount of drug was added to each vial and mixed by using vortex mixer. These mixtures were kept at 25 c for 72 hours on a rotary shaker to reach equilibrium. The equilibrated samples were removed from shaker and centrifuged at 3000 rpm for 15 min to separate undissolved drug. The supernatant was taken and filtered through 0.45mm filter. Aliquots of supernatant were diluted with methanol and analyzed for dissolved drug by UV Spectrometry.

Pseudo ternary phase diagram:

To determine the concentration zone of components of micro emulsions, Pseudo ternary phase diagrams of oil, surfactant was constructed using water titration method at room temperature.

Based on solubility study of drug in oil, surfactant, co surfactant and aqueous phase grouped in to four different combinations for studies. Surfactant and co-surfactant were blended in different weight ratio. The mixture of surfactant and co-surfactant was mixed with the oil at different weight ratios. Titration was done by adding small amount of water in 5% increment to each mixture with mechanical shaking by vortex mixture.

The samples kept aside for equilibration. After equilibration, the samples were visually observed for transparency and classified as coarse, clear and micro emulsions.

Preparation of Liquid SNEDDS

The surfactant/co-surfactant ratio and oil/S/CoS ratio was selected from the ternary phase diagram. A series of formulation were prepared by different concentrations of oil, surfactant and co-surfactant. The oil and surfactant were weighed in suitable

properties and drug was dissolved in this mixture by using vortex mixture and stored at room temperature until further use.

Preparation of Solid SNEDDS

S-SNEDDS was prepared by mixing selected liquid SNEDDS containing Repaglinide with Neusilin US2 in 2:1 proportion. The liquid SNEDDS of Repaglinide was adsorbed onto Neusilin US2 by physical mixing in a small mortar and pestle. Resultant damp mass was passed through sieve no. 120 and dried at ambient temperature.

Dispersibility test

In this method, a predetermined volume of formulation (0.2 ml) was introduced into 300 ml of water in a glass beaker that was maintained at 37°C, and the contents mixed gently using a magnetic stirrer. The tendency to emulsify spontaneously and progress of emulsion droplets were observed. The tendency to form emulsion was judged qualitatively and graded as per given in the table 1

Table 1: Assessment of Self Emulsification

| Grade | Dispensability and appearance | Time of Self emulsification (min) |
|-------|--|-----------------------------------|
| A | Rapidly forming micro emulsion, having a clear or bluish appearance | < 1 |
| B | Rapidly forming, slightly less clear emulsion, having a bluish white appearance | < 2 |
| C | Fine milky emulsion | < 2 |
| D | Dull, grayish white emulsion having slightly oily appearance that is slow to emulsify | > 3 |
| E | Formulation, exhibiting either poor or minimal emulsification with large oil globules present on the surface | > 3 |

Droplet size analysis and Zeta Potential

Droplet size was an important factor in self emulsification performance because it determines the rate and extent of drug release, as well as stability of the emulsion. Zeta potential used to identify the charge of the droplets. The magnitude of zeta potential was an indication about stability of colloidal system. The droplet size and zeta potential of emulsion were determined by photon correlation spectroscopy which analyses the fluctuations in light scattering due to Brownian motion of particles by using a zetasizer. Light Scattering was monitored at 25° c at an angle 90°.

Thermodynamic Stability studies¹⁵

To evaluate stability of formulations Centrifugation, freezing and thawing cycles were used. All formulations were kept at -4° C for 24 hours and then kept at 40°c for 24 hours and the cycle was repeated 3 times. Then samples were centrifuged for 30 minutes with 5000 rpm and observed phase separation.

Phase separation

Phase separation study showed that all formulations subjected for this study were stable in 0.1N HCl and distilled water. No signs of phase separation within 2 hours, which indicates formation of stable emulsion.

% Transmittance

1 mL of Liquid SNEDDS was diluted to 100 mL distilled water and observed for any turbidity and % transmittance of the system was measured at 593 nm using UV spectrophotometer keeping distilled water as blank.

Dissolution Studies

Drug release Studies from Liquid SNEDDS were performed using USP XXIV, dissolution apparatus II. The formulations were filled in capsules and introduced into a dissolution apparatus containing 100 ml of 0.1N HCl at 37±0.5°c.

The speed of the paddle was adjusted to 50 rpm. At predetermined time intervals 5, 10, 15, 30, 45 and 60 min, an aliquot (5 ml) of the sample was collected and replaced by equal volume of temperature equilibrated medium. The samples were filtered and analyzed spectrophotometrically at 232 nm.

Characterization of Solid SNEDDS

Angle of Repose

The fixed funnel method was employed to measure the repose angle of SNEDDS. A funnel was secured with its tip at a given height, H above a graph paper that was placed on a flat horizontal surface. The SNEDDS were carefully poured through the funnel until the apex of conical pile just touched the tip of the funnel. The radius, R, of the base of the conical pile was measured. The angle of repose (θ) was calculated using the following formula

$$\theta = \tan^{-1} H/R$$

Where θ = Angle of repose, H = Height of pile and R = Radius of pile

Bulk density, Tapped density, Compressibility Index and Hausner Ratio

1 gm of material was subsequently introduced into a dry 25 ml cylinder, without compacting, the SNEDDS were carefully leveled without compacting and the unsettled apparent volume, V_0 , was read. After carrying out the procedure as given in the measurement of bulk density the cylinder containing the SNEDDS were tapped using a mechanical tapped density tester. Initially the cylinder was tapped 500 times followed by an additional tap of 750 and 1250 times until difference between succeeding measurement was less than 2% and tapped volume, V was measured to the nearest graduated unit. The bulk density and tapped density was calculated, in g/mL, using the formulae

$$\text{Bulk Density (BD)} = \text{Weight of powder} / \text{Volume of Packing}$$

$$\text{Tapped Density (TD)} = \text{Weight of powder} / \text{Tapped Volume of Packing}$$

The Compressibility index (Carr's index, CI) and Hausner's ratio are measures of the propensity of SNEDDS to be compressed. As such, they are measures of the relative importance of interparticulate interactions. In free-flowing SNEDDS such interactions are generally less significant, and the bulk and tapped densities will be closer value. For poor flowing materials, there are generally greater interparticle interactions, and thus a greater difference between the bulk and tapped densities will be deserved. These differences are reflected in the compressibility Index and the Hausner Ratio which are calculated using following formulae

Carr's Compressibility Index (CI) = (TD-BD) / TD X 100

Hausner's Ratio = TD / BD

Drug content determination:

Repaglinide content in S-SNEDDS was estimated using the UV method. S-SNEDDS was dissolved in sufficient quantity of methanol. The solution was sonicated for 10 minutes for extraction of the drug in methanol and filtered. The absorbance of filtrate was read at 232 nm on UV- Visible Spectrophotometer and absorbance was recorded¹⁶.

Drug excipient Compatibility study

IR spectroscopy was conducted using a FTIR spectrophotometer and spectrum was recorded in region of 4000 to 400 cm⁻¹. Solid samples were mixed with potassium bromide and compressed into discs by applying pressure. The compressed disc was placed in light path and the spectrum was obtained.

In Vitro Drug release Study

In vitro dissolution study of S-SNEDDS and pure drug were carried out using USP type-2 dissolution test apparatus in 100 mL of 0.1N HCl at 37±0.5°C with 50 rpm rotating speed. Samples of 5 mL were with-drawn at regular time interval of 5, 10, 15, 30, 45 and 60 min and filtered using 0.45µm filter. An equal volume of dissolution medium was added to maintain the volume. Drug content from sample was analyzed using UV-spectrophotometer at 232 nm.

RESULTS AND DISCUSSIONS

Solubility Studies

Solubility studies were performed to identify suitable oil, surfactant and co-surfactant that possess good solubilizing capacity for Repaglinide. Identifying the suitable oil, surfactant/co-surfactant having maximal solubilizing potential for drug under investigation is very important to achieve optimum drug loading and also to minimize the final volume of SNEDDS. The solubility of drug was tested in different oils, surfactants and co-surfactants. Among the used oils the olive oil and Miglyol showed maximum solubility. Amongst various surfactants that were screened, Cremophore RH 40 exhibited good solubilization for Repaglinide where as amongst

various co-surfactants, Capryol 90 and Labrasol exhibited highest solubilizing potential for Repaglinide

Pseudo ternary phase diagram

Pseudo ternary phase diagrams were constructed for each surfactant/co-surfactant combination.

Pseudo ternary phase diagram is used to identify the nanoemulsion region. The self emulsification region was determined by visual observation for spontaneity of emulsification, clarity, color and stability. From the phase diagrams it was inferred that increase in oil content increased the particle size proportionally and resulted in coarse emulsions. With the decreasing of co-emulsifier concentration, the area decreased slightly. Self-nanoemulsifying formulations could be obtained under the condition of surfactant: co-surfactant ratio from 3:1 to 4:1, and oil: (Surfactant: co-surfactant) ratio equal to 1:9, 2:8.

Characterization of Liquid SNEDDS

Dispersibility test

The *in-vitro* performance of SNEDDS was visually assessed using the grading system and it was found that, SNEDDS rapidly formed micro emulsion within 1 min which was clear and slightly bluish in appearance as per grade A

Droplet size analysis and Zeta Potential

Droplet size distribution and zeta potential of SNEDDS were determined by using zetasizer and results shown in Table 1. The mean droplet size was relatively smaller for SNEDDS formulations containing olive as oil phase, Cremophore RH 40 as surfactant, and Capryol 90 as co-surfactant than the other formulations. The results from zeta potential analyses of all four formulations are summarized in Table 1. Electrostatic forces of nanoemulsion droplets are critical for assessing the stability of the SNEDDS formulation. Several studies have reported that the zeta potential played an important role in the interactions of formulation components with mucus of the gastrointestinal tract¹⁷. An increase in the electrostatic repulsive forces between nanoemulsion droplets prevents the coalescence of nanoemulsion droplets, and a decrease of electrostatic repulsive forces will result in phase separation.

Table 2: Droplet Size and Zeta potential of SNEDDS

| Formulation | Droplet Size (nm) | Zeta Potential (mV) |
|----------------|-------------------|---------------------|
| F ₁ | 2.6 | -21.7 |
| F ₂ | 2.8 | -17.6 |
| F ₃ | 9.9 | -22.3 |
| F ₄ | 4.4 | -16.4 |

Table 3: Cumulative % drug release of SNEDDS and plain drug

| Time | F ₁ | F ₂ | F ₃ | F ₄ | Plain drug |
|------|----------------|----------------|----------------|----------------|------------|
| 5 | 14.7 | 11.5 | 12.5 | 9.54 | 10.7 |
| 10 | 21.3 | 17.6 | 19.1 | 14.2 | 28.2 |
| 15 | 32.5 | 29.5 | 28.3 | 25.7 | 37.6 |
| 30 | 72.6 | 68.1 | 66.5 | 64.3 | 46.5 |
| s45 | 86.3 | 77.3 | 81.5 | 73.5 | 52.3 |
| 60 | 98.1 | 91.2 | 95.5 | 86.1 | 61.9 |

Thermodynamic Stability studies: The thermodynamic stability study was performed by using freezing, thawing and Centrifugation methods. On the basis of thermo dynamic stability studies it was found to be all formulations were passed and selected for further characterization.

Phase separation: Phase separation was performed with excess of water, standard phosphate buffer PH 6.8 and 0.1N HCl and was stored for 12 hours. It was found to be, all formulations didn't show any sign of precipitation or phase separation and are thus, said 'robust to dilution'¹⁸.

Percentage Transmittance: Percentage transmittance proved the transparency of formulation. All the formulations have % transmittance above 99.9%. Hence all the formulations were clear.

Dissolution Studies

Dissolution studies were performed for SNEDDS and pure drug. Drug release from all formulations was found to be higher as compared with that of pure drug (figure 1). The in vitro dissolution studies clearly depicts that there is approximately increase in dissolution rate of liquid SNEDDS when compared to pure drug, it may be contributed to the fact that the drug in liquid SNEDDS was already in dissolved form, and also the size of SNEDDS was in the range of 10 nm. Results were shown in table 3

Characterization of Solid SNEDDS

Angle of Repose

The angle of repose of the solid SNEDDS was determined by funnel method. The angle of repose of S₁ and S₂ was found to be 24.2 and 21.8 respectively which was an indication of good flow properties (Table 4).

Bulk Density, Tapped Density, Compressibility Index and Hausner Ratio

Bulk density and tapped density of S₁ and S₂ formulations were found to be 1.25, 1.53, 1.38 and 1.72 respectively. Carr's index of S₁ and S₂ was found to be 18.3 and 19.2 respectively which indicated good compression. Hausner's ratio was determined for characterization of powder flow of S-SNEDDS. Hausner's ratio for S₁

and S₂ was less than 1.25 was considered to be indication of good flowability (Table 4).

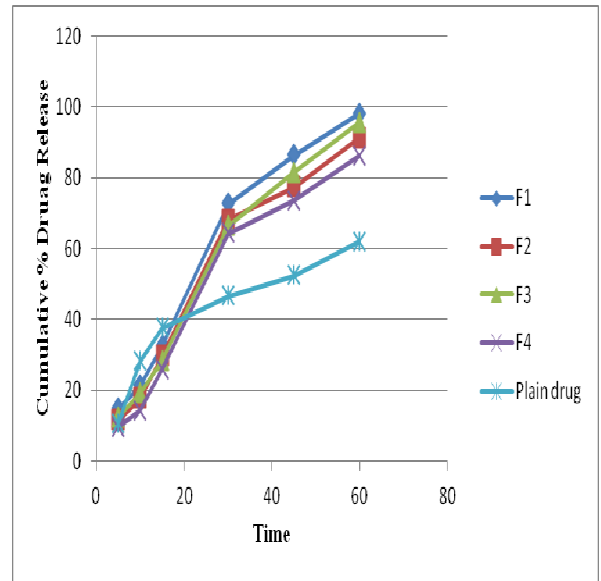


Fig. 1: In-vitro drug release profiles of formulations F₁, F₂, F₃, F₄ compared with Pure drug in 0.1N HCl

Table 4: Micromeritic properties of S-SNEDDS

| Micromeritic properties | S ₁ | S ₂ |
|-------------------------|----------------|----------------|
| Angle of repose | 24.2 | 21.8 |
| Bulk density | 1.25 g/ml | 1.38 g/ml |
| Tapped density | 1.53 g/ml | 1.72 g/ml |
| Carr's index | 18.3 | 19.7 |
| Hausner's ratio | 1.22 | 1.24 |

Drug content determination

Repaglinide content in S-SNEDDS was estimated using the UV method. Drug content in S₁ and S₂ was found to be 88.9% and 86.8% respectively.

Drug excipient Compatibility study

FT-IR spectra are mainly used to determine interaction between the drug and any of the excipients used. The presence of interaction is detected by the disappearance of important functional group of the drug. Repaglinide has characteristic absorption peaks at 3026.71cm⁻¹, 1688cm⁻¹, 1586.86cm⁻¹, 1566.80cm⁻¹, 1148cm⁻¹, 3097cm⁻¹ and 3413.19cm⁻¹ respectively. Similar peaks were observed in spectra of S-SNEDDS, along with absence of interfering peaks indicating there is no unwanted reaction between Repaglinide and other excipients used in the study.

Table 5: % Cumulative drug release of S-SNEDDS and Plain drug

| Time | S ₁ | S ₂ | Plain drug |
|------|----------------|----------------|------------|
| 5 | 18.3 | 20.6 | 10.7 |
| 10 | 34.5 | 36.3 | 28.2 |
| 15 | 49.2 | 51.8 | 37.6 |
| 30 | 68.6 | 72.5 | 46.5 |
| 45 | 86.1 | 89.6 | 52.3 |
| 60 | 95.4 | 93.1 | 61.9 |

In-vitro drug release study

Dissolution study was performed with S-SNEDDS and pure drug. Cumulative % drug release of SNEDDS S₁ and S₂ drug in 0.1N

HCl was found to be 95.4% and 93.1% respectively and that of plain drug was found to be 61.9% (Table 5). This showed that drug releases from S-SNEDDS was found to be significantly higher as compared to plain drug (Figure 2).

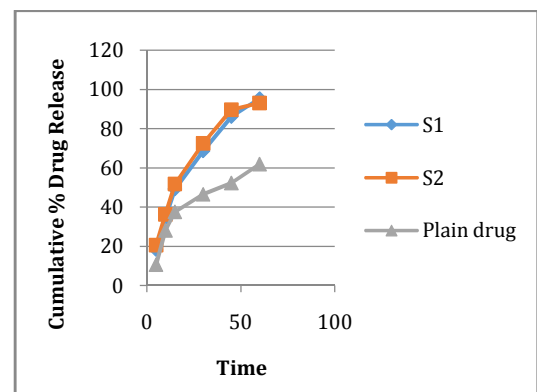


Fig. 2: Cumulative drug release of S-SNEDDS compared with Plain drug in 0.1N HCl

CONCLUSION

An optimized Repaginate loaded formulation consisting of Olive oil (19.8%), Cremophore RH 40 (62.2%), Capryol 90 (16.6%) and Miglyol (9.6%), Cremophore RH 40 (74.3%), Labrasol (15.7%), the compositions are selected based upon the dispersibility test and

solubility studies. From droplet size analysis it is concluded that the formulation belongs to SNEEDS and the dissolution of SNEDDS form of Repaginate showed complete and faster dissolution profile compared to pure drug and equal to marketed formulation. Thermodynamic stability studies indicate there is no phase separation.

The optimized liquid SNEDDS formulation based on droplet size and dissolution study of SNEDDS was converted into solid SNEDDS by considering some drawbacks of SNEDDS. The dissolution characteristics of solid intermediates of SNEDDS filled into hard gelatin capsules was investigated and compared with liquid formulation. The results indicated that solid intermediates showed comparable rate and extent of drug dissolution in a discriminating dissolution medium as liquid SNEDDS indicating that the self-emulsifying properties of SNEDDS were unaffected following conversion. Thus our studies conformed that SNEDDS can be used as a possible alternative to conventional oral formulation of Repaglinide.

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