

Self-Nanoemulsifying Drug Delivery System to Enhance Solubility and Dissolution of Lipophilic Drug Repaglinide

Pathuri Raghuvver, A. Prameela Rani

Department of Pharmaceutics, University College of Pharmaceutical Sciences, Acharya Nagarjuna University, Guntur, Andhra Pradesh, India

Abstract

Introduction: Self-nanoemulsifying drug delivery systems (SNEDDSs) are isotropic mixture of oil, surfactant, cosurfactant, and drug that form fine oil in water emulsion when get contact with water on mild agitations. This property renders the SNEDDS into perfect drug delivery systems to deliver Biopharmaceutics Classification System Class II drugs with enhanced solubility. **Materials and Methods:** The SNEDDSs have different preparation methods, classified as high-energy method and low-energy methods. In low-energy method, phase inversion method or standard admixture method using vortex mixture was used to prepare formulations using various oils and surfactants. **Results:** Solubility of repaglinide was carried out in different vehicles; we observed that high solubility was found in neem oil (45 mg/mL), Cremophor RH 40 (21 mg/mL), Transcutol (48 mg/mL), and Span 80 (34 mg/mL). Ternary diagrams were drawn for oil:Smix ratios which were clear emulsion observed. From the phase diagrams, ratios possessing high oil percentage were considered, F1 to F7 formulation ratios were selected. All formulations were subjected to evaluation tests with no phase separation, no precipitation. F1 and F7 formulation has shown high *in vitro* drug release when compared with other formulations by forming nanosize particle 223 nm and 221nm, respectively. **Conclusion:** Repaglinide SNEDDSs have shown 157% increase in *in vitro* dissolution data when compared to marketed formulation.

Key words: Cremophor RH 40, repaglinide, SNEDDS, solubility enhancement

INTRODUCTION

We all known that the solubility and permeability are the main barriers for drug absorption through orally for Class II and IV of biopharmaceutical classification drug systems, (Biopharmaceutics Classification System [BCS] Class II and IV).^[1] BCS Class II drugs majorly suffer with intra- and inter-subject variability, low bioavailability, and lack of dose proportionality.^[2] To overcome the problems, various strategies are developed such as increased usage of surfactant, cyclodextrins, solid lipid nanoparticles, permeation enhancers, and lipid drug delivery systems.^[3]

Lipid-based drug delivery systems came to action for the BCS Class II and IV, several methods are developed in that one is self-nanoemulsifying drug delivery systems (SNEDDSs) to enhance the bioavailability by increasing solubility and dissolution.^[4] Using SNEDDS, the bioavailability is increased by several mechanisms in that few are increased drug solubilization, increased

membrane permeation, lymphatic transport, and inhibition of P-gp which are the main contributions.^[5,6]

SNEDDSs are isotropic mixture of oil, surfactant, cosurfactant, and drug that form fine oil in water emulsion when get contact with water on mild agitations.^[7] This property renders the SNEDDS into perfect drug delivery systems to delivery lipophilic or poor aqueous soluble drug through oral route by solubilizing drug in oil or oil/surfactant blend.^[8]

In process of self-emulsification in stomach, the drug was present as small oil droplet, leading to improved solubility

Address for correspondence:

Pathuri Raghuvver, Department of Pharmaceutics, University College of Pharmaceutical Sciences, Acharya Nagarjuna University, Guntur - 522 510, Andhra Pradesh, India. Phone: +91-9177230111. E-mail: prvrpharma88@gmail.com

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their by increasing dissolution through providing a large interfacial area for portioning the drug between oil and gastrointestinal tract (GIT) fluids.^[9] Other advantages of SNEDDS are increased stability of drug and had a chance to supply the finished product into capsule dosage form.^[4] The drugs which having rate limiting step as absorption, lipid-based drug delivery systems have a possibility for enhancing rate and extent of drug absorption and reproducible plasma concentration profile can be obtained.^[10,11]

Repaglinide was approved by Food and Drug Administration in 1997. It is carbamoylmethyl benzoic acid derivative and nateglinide, a Dphenylalanine derivative, according to classification, it belongs to oral hypoglycemic agents known as the meglitinide analogs. We all known that diabetes is classified into two types: Type I and Type II. It was particularly developed to control meal-related glucose fluctuations in patients diagnosed in type 2 diabetes. They control glucose level by stimulating insulin secretion.^[12]

The main objective is to design, formulate, and evaluate SNEDDS using repaglinide as drug to increase the solubility and dissolution profile.

MATERIALS AND METHODS

Materials

Repaglinide was obtained as gift sample from Aurobindo Pharma, Vizag, Andhra Pradesh. Neem oil was purchased from Shree Biotech and Inputs, Mandasaur, Madhya Pradesh. Corn oil was obtained from Deve Herbes, Delhi. Cremophor RH 40 was purchased from Yarrow Chemicals Pvt. Ltd., Mumbai. Brij 35 and Span 80 were obtained from Loba Chemicals, Mumbai. Transcutol P was purchased from Avra Synthesis, Hyderabad.

Methods

Solubility

The solubility of repaglinide in various oils, surfactant, and cosurfactant was done. An excess amount of drug was dissolved in 2 ml of oil, surfactant, and cosurfactant individually in a screw-capped vials. These vials are subjected to mixing for 72 h. After completion of time, the oil was subjected to centrifuge at 2500 rpm for 20 min. The supernatant was taken and diluted with methanol subjected to ultraviolet (UV).^[13]

Construction of ternary phase diagrams

Using ternary diagrams, we can obtain self-nanoemulsifying region with ratio of oil and surfactant to form nanoemulsion. Ratios of self-nanoemulsifying region form nanoemulsion spontaneously with dilution under gentle agitation. The

ternary phase diagram was constructed by water titration method. The diagram was constructed by giving input of S-mix ratio and oil concentrations obtained from preliminary trails conducted from S-mix ratio 1:1 to 1:9 and 2:1 to 9:1 mixed with 0.1 mL of oil, diluted with water the ratios which form clear nano solution without any coalescence of oil are considered as good ratios. This diagram helps to get good emulsifying ratios for nanoemulsion.^[14]

Preparation of SNEDDS

The preparation was done under normal room temperature. This method was developed by Forgreini. SNEDDSs were prepared using screened ratios obtained from ternary diagrams to measure accurately oil, surfactant, and cosurfactant. Drug was dissolved in oil and mixed with surfactant mixture kept on cyclo mixture with optimum Rpm for few minutes up to clear solution.^[15]

Characterization

Percent transmittance

Repaglinide SNEDDSs were reconstituted with distill water and the resulting nanoemulsion was subjected to visual observation for any turbidity. The formed nanoemulsion was measured percent transmittance using UV spectrophotometer at 638.2 nm using against distill water as blank.^[16]

Self-emulsification time (SET)

The undiluted SNEDDSs were used to perform self-emulsification time. In this test, we are using dissolution apparatus type II. Dissolution vessel was filled with 500 mL of distill water at temperature of 37°C and maintain agitation at 50 Rpm. The time required to form nanoemulsion was noted. According to time and appearance of solution, they are classified into five grades from Grade A to Grade E.^[17]

- A: Rapidly forming (within 1 min) nanoemulsion, having a clear or bluish appearance.
- B: Rapidly forming slightly less clear emulsion having a bluish-white appearance.
- C: Fine milky emulsion that formed within 2 min.
- D: Dull, grayish-white emulsion having slightly oily appearance that is slow to emulsify (longer than 2 min).
- E: Formulation, exhibiting either poor or minimal emulsification with large oil globules present on the surface.

Grade A and B formulation will remain as nanoemulsion when dispersed in GIT, while formulation falling in Grade C could be recommended for SEDDS formulation.^[18,19]

Phase separation

The reconstituted SNEDDS was subjected to centrifuge at 3000 Rpm for 30 min. The formulation was checked any phase separation, creaming, and cracking. Failed formulations were rejected because they are instable in nature.^[20]

Optical clarity

The reconstituted SNEDDS was subjected to optical clarity for 24 h. After formation of nanoemulsion, optical clarity was checked using UV at 0, 12, and 24 h at 638.2 nm using water as blank. The formulations form any turbidity they are rejected.^[21]

Cloud point

The screened formulations are diluted in water in ratio 1:100 and placed in a water bath. Increase the temperature of water bath, while heating gentle agitation was provided by glass rod. At which temperature, the cloudiness appearance was measured.^[22]

Dispersibility

In this dispersibility test, the undiluted form of SNEDDS is filled in capsule. The efficiency of self-emulsification was assessed using a standard USP XXII dissolution apparatus 2.^[23] A 1 mL of each formulation was added to 500 mL of distilled water, 0.1 N HCl, and 6.8 phosphate buffers (PB) at $37 \pm 0.5^\circ\text{C}$. A standard stainless steel dissolution paddle rotating at 50 rpm provided gentle agitation.^[24] According to the appearance of solution, they are classified into five grades from Grade A to Grade E.

Grade A and B formulation will remain as nanoemulsion when dispersed in GIT, while formulation falling in Grade C could be recommended for SEDDS formulation.^[18]

Particle size and polydispersibility index (PDI)

The average droplet size and PDI of SNEDDSs were measured by photon correlation spectroscopy using a Malvern Zetasizer (Nano ZS90, Malvern Instruments Ltd., UK) with a 50 mV laser. The formulation (0.1 mL) was dispersed in 100 mL of water under gentle stirring in a glass beaker. A 1 mL aliquot was withdrawn and added into a sample cell for droplet size measurement.

In vitro drug release profile

The SNEDDSs were subjected to *in vitro* drug release profile to identify the drug release pattern. *In vitro* drug release study was carried out for screened formulation, marketed drug, and pure drug by conventional method. HPMC capsule size "00" filled with SNEDDS separately was put in 900 mL of 7.4 PB at 50 rpm and $37 \pm 0.5^\circ\text{C}$ using USP II apparatus. At predetermined time interval, aliquots of samples (5 mL) were collected and filtered through membrane filter, suitably diluted and analyzed spectrophotometrically at 243 nm. The *in vitro* dissolution data were analyzed and cumulative percentage drug release was plotted against time.

RESULTS AND DISCUSSION

Solubility

Solubility in oils

Solubility is an important parameter to select excipients for formulation. Different oils were used in solubility; they are neem oil, corn oil, cotton seed oil, and papaya seed oil. The values of solubility are presented in Table 1. Among all neem oils have high concentration next to corn oil. Hence, neem and corn oils are considered for developing formulation.

Solubility in surfactants

Solubility is the preliminary screening of excipients for formulation. In that, different surfactants are used in solubility study of repaglinide drug. The values are represented in Table 2. Among all surfactants, Cremophor RH 40 and Tween 20 had shown high solubility of drug.

Solubility in cosurfactants

Different cosurfactants are selected for solubility. The values of cosurfactant after centrifugation are listed in Table 3. Among all the cosurfactants, Transcutol and Span 80 have shown high solubility of drug, they are selected for formulation.

Table 1: Solubility studies of repaglinide in various oils

Oil	Solubility (mg/mL)
Neem oil	45.03± 0.59
Corn oil	14
Papaya seed oil	13.06± 0.53
Cotton seed oil	7.47 ± 1.12
Castor oil	8.74±1.74
Almond oil	5.49±0.89

Table 2: Solubility studies of repaglinide in various surfactants

Surfactant	Solubility (mg/mL)
Cremophor RH 40	21
BRIJ 35	10
Tween 20	11
Span 20	2

Table 3: Solubility studies of repaglinide in various surfactants

Surfactant	Solubility (mg/mL)
Transcutol	48
Span 80	34.08±0.45
Tween 80	3.34±0.87
PEG 400	5.21±1.02

Construction of ternary phase diagrams

The self-emulsification process of individual formulation depends on the individual concentration of oil, surfactant, and cosurfactant. The diagram was constructed to identify good emulsifying region. It is a clear isotropic region which was identified by optical observation and helps in selecting ratio of excipients.^[25]

From the solubility data, neem oil was selected for formulation, Cremophor RH 40 and Brij 35 were selected as surfactant, Transcutol and Span 80 were selected as cosurfactant. The oils are titrated with different Smix ratio from 1:1 to 1:9 and 2:1 to 9:1. The neem oil has ability to form clear nanoemulsion when mixed with Smix of Cremophor RH 40 and Span 80 forms nanoemulsion at 4:1–7:1 and subjected to ternary diagrams [Figure 1-5]. From the ternary phase diagrams, seven formulation ratios were selected and presented in Table 4.

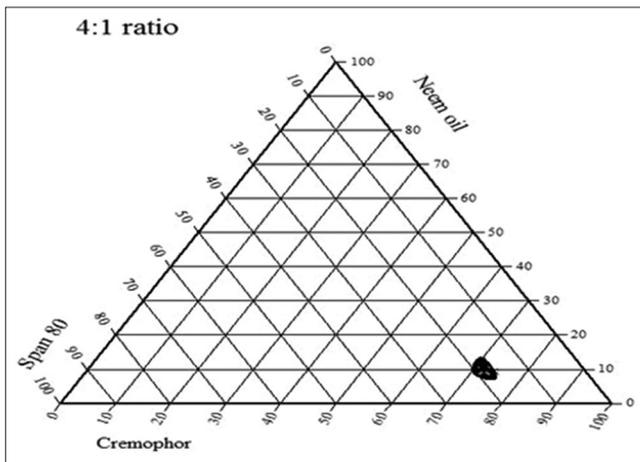


Figure 1: Pseudoternary phase diagram of neem oil with Cremophor RH 40:Span 80 (4:1)

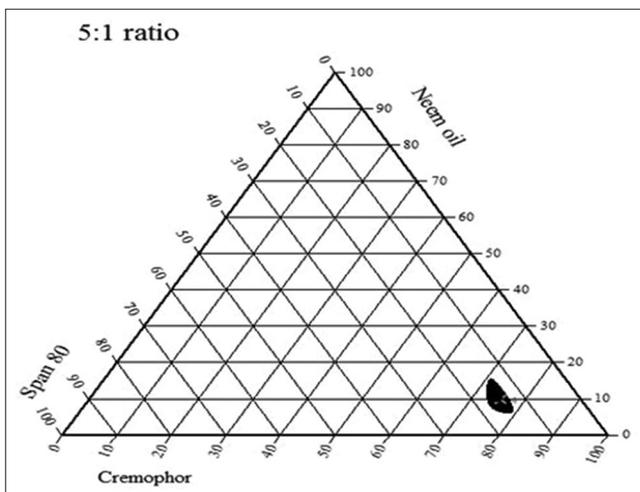


Figure 2: Pseudoternary phase diagram of neem oil with Cremophor RH 40:Span 80 (5:1)

Percent transmittance

All selected formulations are subjected to percent transmittance and values are presented in Table 5. The values of percent transmittance show F1, F2, F6, and F7 highest percent transmittance. The value which is >98% shows that the particles present in formulation are in nanometric scale. These formulations have more efficiency to form SNEDDS.

SET

SET proves that efficiency of ratio to form nanoemulsion on mild agitations. The time required to form emulsion are represented in Table 6. From the percent transmittance values, the four formulations are subjected to SET. SET will explore time needed for emulsification process under gentle mixing, in addition to it will also ensure no further precipitation of dispersed o/w emulsion. From the SET values we can observe that, increase in surfactant concentration leads to high SET which shows delay in dispersion of formulation. Cremophor

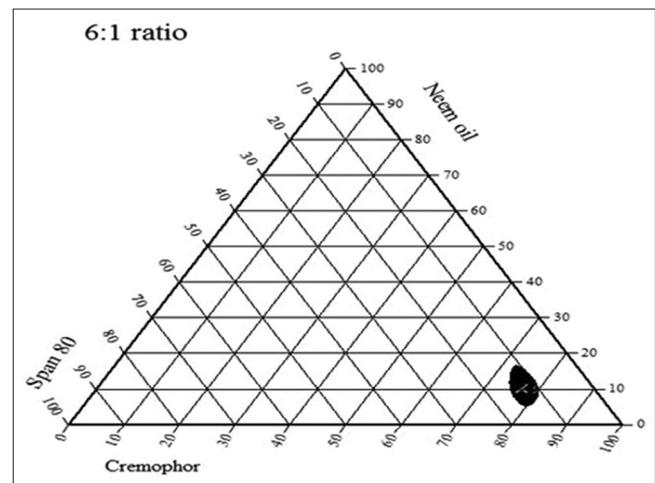


Figure 3: Pseudoternary phase diagram of neem oil with Cremophor RH 40:Span 80 (6:1)

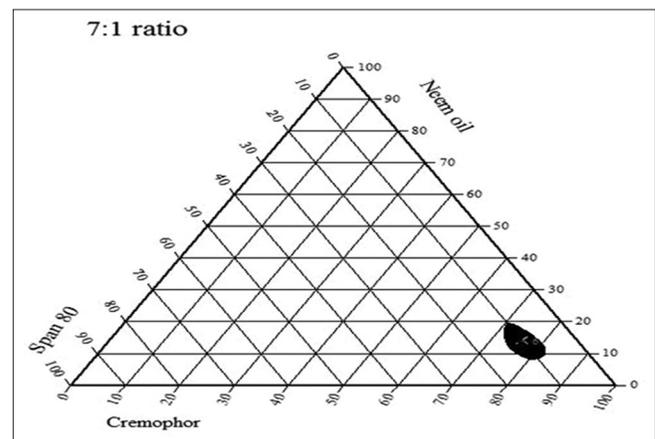


Figure 4: Pseudoternary phase diagram of neem oil with Cremophor RH 40:Span 80 (7:1)

RH 40 was used as surfactant in formulation when it gets contact with water it form gel-like intermediate structures which forms nanoemulsion very slowly.^[26]

Phase separation, cloud point, and precipitation

After the formation of emulsion, there must be no phase separation. We observed that there are no phase separation and no precipitation in formulations. The cloud point is measurement at which temperature the clear solution turns into cloudiness. It occurs due to dehydration of polyethylene group of the non-ionic surfactants with a resulting decrease in the surfactant hydrophilic-lipophilic balance values. The cloud points of all formulations are very high, thus sufficiently stable when after administration into body.^[27,28] The values of cloud point and phase separation are presented in Table 7.

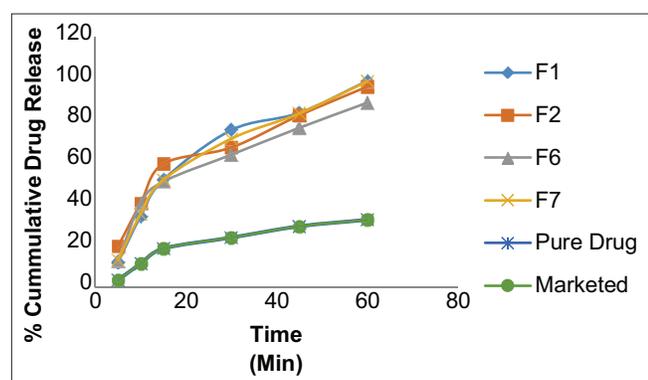


Figure 5: *In vitro* drug release profile

Table 4: Selected ratios from ternary phase diagrams

Code	Neem oil	Surfactant (Cremophor RH 40)	Cosurfactant (Span 80)
F1	12	71	17
F2	13	70	17
F3	9	70	21
F4	11	71	18
F5	15	74	11
F6	11	78	11
F7	15	71	14

Table 5: Values of percent transmittance

Code	Values of percent transmittance
F1	99.2
F2	98.3
F3	83.4
F4	88.9
F5	94.3
F6	90.2
F7	95.4

Particle size

Formulations showing high % transmittance (F1, F2, F6, and F7) were subjected to droplet size determination of dispersed. The results are given in Table 8 showing that all the formulations were in nanometer size range. PDI which reflects uniformity of diameter was also found to be low, indicating most of the dispersed phase present in nano size. The droplet size of formulations is a very important parameter because it decides rate and extent of drug release which will dictate drug absorption of repaglinide. It is observed that formulations were having small droplet size which results in possessing larger surface area, larger surface area leads to enhanced drug dissolution there by enhanced drug absorption.^[29]

In vitro drug release profile

Different repaglinide SNEDDS formulations were filled in hard gelatin capsules which were explored for their *in vitro* dissolution profile along with marketed tablet formulation and pure repaglinide filled in capsule. The results are presented in Table 9. The *in vitro* drug release profile for SNEDDS is superior to pure drug and marketed formulation. In dissolution study, we seen that at end of the 1 h, only 62.9% and 32.28% were released from the marketed and pure drug, but SNEDDS formulae showed enhanced release in the same

Table 6: Self-emulsification time

Code	SET (s)	Grade
F1	80±1.3	B
F2	77±2.67	B
F6	95±2	B
F7	104±3	B

Table 7: Phase separation, cloud point, and precipitation

Code	Phase separation	Cloud point	Precipitation
F1	X	79±1.11	XX
F2	X	84±1.34	XX
F6	X	84±1.34	XX
F7	X	80±1.78	XX

*x: No phase separation, **xx: No precipitation

Table 8: Particle size and PDI

Formulation code	Avg. particle size (nm)	PDI
F1	223	0.357
F2	246	0.384
F6	289	0.404
F7	221	0.348

PDI: Polydispersibility index

Table 9: *In vitro* drug release profile

Formulation code	Time (min)					
	5	10	15	30	45	60
F1	11.96±0.1	34.09±0.8	51.46±0.34	75.324±0.25	83.59±0.45	98.983±0.15
F2	19.47±0.1	40.31±0.21	59.17±0.18	66.96±0.37	82.38±0.16	96.17±0.29
F6	12.56±0.14	41.08±0.12	50.64±0.24	63.5±0.32	76.39±0.21	88.42±0.16
F7	13.07±0.11	35.1±0.25	51.45±0.11	71.19±0.24	83.26±0.32	98.69±0.19
Marketed	9.72±0.2	19.354±0.34	30.65±0.43	49.58±0.13	54.52±0.32	62.98±0.12
Pure drug	03.41±0.1	11.27±0.14	18.49±0.39	23.75±0.25	29.16±0.17	32.28±0.23

*n=6

time period. More than 95% of repaglinide was released from the F1, F2, and F7 formulation. Repaglinide dissolved and released from SNEDDS reached $98.983 \pm 0.15\%$ for formula F1, $96.17 \pm 0.29\%$ for formula F2, $88.42 \pm 0.16\%$ for formula F6, and $98.69 \pm 0.19\%$ for formula F7 within the 1h. This enhancement *in vitro* release rate and extent of repaglinide could be attributed to nanometric droplet size and spontaneous emulsification, which can be correlated to particle size analysis and % transmittance values. Along with the particle size, presentation of repaglinide in dissolved state also leads to enhancement of solubility, thereby increase in extent of dissolution. Among all formulations, F6 has exhibited decrease in extent of release when compared to other optimized formulations. This may be due to the higher surfactant concentration. This higher amount of surfactant resulting migration of certain surfactant into surrounding aqueous medium on dispersion. This migrated surfactant leads to the formation of micelles that can trap free drug resulting decreased drug release.^[30]

CONCLUSION

Formulation of repaglinide in SNEDDS can increase the solubility of drug which is responsible for its low bioavailability. In the present study we can observe that characteristics of formulation mainly depends on concentration and properties of formulation ingredients. Repaglinide SNEDDS formulated with neem oil, Cremophor RH 40 and Span 80 have shown 157% increase in *in-vitro* dissolution data when compared to marketed formulation which can be attributed to its small droplet size.

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