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RESEARCH ARTICLE

OPTIMIZATION OF SELF-NANOEMULSIFYING DRUG DELIVERY SYSTEM (SNEDDS) OF REPAGLINIDE USING D-OPTIMAL MIXTURE EXPERIMENTAL DESIGN

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ABSTRACT

Repaglinide, which is widely used in treatment of type 2 diabetes, is practically insoluble in water with low bioavailability (about 50%) and poor absorption characteristics in upper intestinal tract. Self-nanoemulsifying drug delivery system (SNEDDS) of repaglinide was developed and optimized using D-optimal mixture design to improve its dissolution and solubility. Suitable combination of excipients was selected by assessing solubility, emulsification efficiency and use of ternary phase diagram. The D-optimal mixture experimental design was applied to optimize formulation containing minimum amount of surfactant, maximum amount of lipid showing enhanced emulsification and dissolution rates. Four formulation variables; the oil phase X1 (Labrafil® M1944CS) and X2 (Capmul® MCM-C8), the surfactant X3 (Tween® 80) and the co-surfactant X4 (Transcutol® P) were used in the design. The prepared eleven formulations were evaluated in vitro for droplet size and % drug release. Formulation F5 was found to be optimum showing 100.05% drug release 53 nm droplet size, 13 s self-emulsification time and robustness to dilution with different media.

KEYWORDS: Repaglinide, SNEDDS, D-optimal design, Poorly water soluble drug

INTRODUCTION:

Repaglinide is widely used in the treatment of non-insulin dependent diabetes mellitus (NIDDM) or type - 2 diabetes[1,2]. It has short half-life and has low bioavailability (50%) and poor absorption characteristics in the upper intestinal tract. Repaglinide is practically insoluble in water; this poor aqueous solubility and low bioavailability may lead to sub-therapeutic achievement[1-4]. So, there is need to improve solubility and dissolution profile by incorporating in Self emulsifying drug delivery system (SNEDDS).

Formulation design can be a useful approach to improve the absorption and thus the oral bioavailability of such drug candidates. In recent years, there was growing interest in lipid-based formulations to improve oral bioavailability of lipophilic drugs. In fact, the most popular approach is the incorporation of the drug compound into inert lipid vehicles such as oils-surfactant dispersions, liposomes, microemulsions, nanoemulsions, with particular emphasis on SNEDDS. The latter systems comprise isotropic mixtures of natural or synthetic oils with surfactants and co-surfactants[5-8]. These systems spontaneously emulsify when exposed to gastro-intestinal (GI) fluids to form oil in water nanoemulsion with nanometric droplet size, in the range of 20-200 nm. SNEDDS exhibited privileges over other delivery systems. They are characterized by excellent stability, circumventing the stability problem of solid lipid nanoparticles and liposomes. Furthermore, SNEDDS can be filled in hard gelatine capsules due to their anhydrous nature enabling its administration as unit dosage form. Therefore SNEDDS would be an effective, convenient and more patient compliant approach in comparison to o/w nanoemulsion[7,8]. The objective of the present study was to optimize SNEDDS of repaglinide using minimum surfactant concentration, to maintain nanosized droplets on dilution by the GI fluids with an aim to increase its solubility and dissolution profile. Formula optimization was based on in vitro assessments. The formulation was tailored to compromise between drug solubility in excipients, ease of emulsification and globule size of the dispersion. Selected formulation exhibiting promising in vitro properties is anticipated to improve oral delivery of the drug.

MATERIALS AND METHODS:

MATERIALS:

Repaglinide was procured. Oleoylmacrogol 6-glycerides (Labrafil® M1944CS), Plurol oleque and diethylene glycol monoethyl ether (Transcutol® P) were donated by Gattefosse Co. (Mumbai). Polyoxy 40 hydrogenated castor oil (Cremophor RH®40) and Polyoxy 35 castor oil (Cremophor® EL) was gift samples from BASF Co.

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(Germany). Capmul® MCM-C8 and Captex® 200 were obtained by Abitec Corp. (USA) as gift samples. Tween® 20 and Tween® 80 were received from Mohini organics (Mumbai) as gift samples. LICAPS® (liquid filled capsules) were donated by ACG capsules (Mumbai). Propylene Glycol (PG), Polyethylene Glycol (PEG), Oleic Acid was purchased from Loba Chemie (Mumbai). Methanol and all other chemicals and solvents used were of analytical grade.

METHODS:

COMPATIBILITY TESTING[9]:

Determination of compatibility between drug and different excipients is an important part of the preformulation stage during the development of a dosage forms. The pure drug sample and formulation of drug with selected excipients were subjected for FTIR analysis (JASCO 4100) using KBr as 1:100 proportion and triturated in mortar pestle and IR spectra were recorded at the scanning range of 4000 to 600 cm^{-1}

DETERMINATION OF SOLUBILITY OF REPAGLINIDE IN OILS, SURFACTANTS AND CO-SURFACTANTS[9]:

The solubility of Repaglinide in various oils (Labrafil® M1944CS, Oleic Acid, Capmul® MCM C8, Captex® 200), surfactants (Cremophor® EL, Cremophor® RH40, Tween® 20, Tween® 80), and co-surfactants (PEG, Propylene Glycol, Transcutol® P) was determined. Excess repaglinide was added to 2 gm of each component and mixture was mixed using a magnetic stirrer and then kept on orbital shaker (Remi motors & RIS-24BL) for 72 h at temperature 37±1.0^{0}C. The samples were then centrifuged at 5,000 rpm for 15 min and analysed by UV spectrophotometer (Shimadzu-1800, Japan).

SURFACTANT EMULSIFICATION STUDY[10]:

The surfactants were screened for their emulsification ability. The oil and surfactant were taken in ratio 1:1. The mixtures were heated at 50 °C on water bath to homogenise solution. 50 mg of formulation was then diluted with 50 ml distilled water. Ease of emulsification was judged by the number of flask inversions required to yield emulsion. The emulsions were allowed to stand for 2 h and their % transmittance was determined at 638.2 nm by UV-spectrophotometer (Shimadzu-1800, Japan) using distilled water as a blank. Emulsions were also observed visually for any turbidity or phase separation.The selected oil and surfactants were further used for screening of the co-surfactants. The mixtures of surfactant, co-surfactant and oil were prepared in the ratio of 2:1:3 and evaluated in a same manner as above.

CONSTRUCTION OF PSEUDO-TERNARY PHASE DIAGRAMS[9]:

A series of formulations were prepared using oil: surfactant ratios (1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, 9:1). A pseudo-ternary phase diagram was constructed by titration of component mixture of oil, surfactant and co-surfactant with water at room temperature. After equilibrium, the mixture was visually observed. The generated sample which was clear or slightly bluish in appearance was determined as nanoemulsion. A series of Pseudo-ternary phase diagrams were constructed to identify the nanoemulsion regions and to optimize concentration of selected formulation variables.

OPTIMIZATION OF REPAGLINIDE SNEDDS USING D-OPTIMAL MIXTURE DESIGN[11]:

Factor	Levels (%w/w)	
	Low	High
X1 (Labrafil® M1944CS)	10	30
X2 (Capmul® MCM-C8)	0	20
X3 (Tween® 80)	30	60
X4 (Transcutol® P)	0	40

Table 1: Levels of excipients used in formulation study

An eleven run, D-optimal mixture design was used in the present study to provide empirical mathematical models to describe the effect of four formulation variables (oils, surfactant and co-surfactant) on the responses taken as % drug release and globule size. The levels of independent variables were selected on the basis of results obtained from preliminary studies on solubility of repaglinide in different oils, surfactants and co-surfactants. The oils, surfactants and co-surfactants showing maximum solubility of drug were chosen as independent variables. The Table 1 shows the independent variables and the levels selected for optimization.

The Design-Expert® software (version 8.1; Stat-Ease, Inc., Minneapolis, MN) was used to construct the

model and select the set of candidate points. These included factorial points (high and low level from the constraints on each factor), centre of edges (points midway between adjacent factorial points), constrain plane centroids, axial check points, and an overall centre point. For completely randomized design, second order polynomial equations were generated that explained the non-linear nature of the response. Results of statistical analysis were considered significant if their corresponding *p*-values were less than 0.05.

Sr. No.	Labrafil® M1944CS (%w/w) (X1)	Capmul® MCM-C8 (%w/w) (X2)	Tween® 80 (%w/w) (X3)	Transcutol® P (%w/w) (X4)
F1	10	20	56.311	13.7
F2	10	11	38.5	40
F3	11.25	1.25	60	27.5
F4	18	20	30	32
F5	20.2	11	47	21.3
F6	21.3	0	38.7	40
F7	25	14.8	60	0
F8	30	0	43	27
F9	30	1	56	12.75
F10	30	20	42	7.63
F11	30	8.83	30	31

Data are expressed as mean ±SD (*n* = 3).

Table 2: The formulations of mixture design

PREPARATION OF REPAGLINIDE SNEDDS[10]:

The chosen oils, surfactant and co-surfactants were mixed by magnetic stirring. After proper mixing, 1 mg of drug per 100 mg was added to the mixture. The mixture was sonicated (Biomedica, BMI-599) at 37 ^{0}C for 10 minutes and allowed to stand at room temperature for 48 h. The weighed quantity of repaglinide SNEDDS was filled in capsule (LICAPS®, Capsule size 0) and used for further evaluations. Table 2 shows compositions of formulations.

EVALUATION PARAMETERS:

DROPLET SIZE ANALYSIS[12]:

The droplet size of SNEDDS was measured by using a Malvern Zetasizer (Nano ZS90, Malvern instruments Ltd., UK) with a 50 mV laser. The measurements were performed at 25 ^{0}C at a fixed angle of 90^0. The formulation (100 mg) was dispersed into 100 ml of water under gentle stirring in a glass beaker. Then a 1 ml aliquot was withdrawn and added into a sample cell for droplet size measurement. Each size value reported was the average of at least three independent measurements.

SELF-EMULSIFICATION TIME DETERMINATION[13]:

In order to determine the emulsification time (the time needed to reach the emulsified and homogeneous mixture, upon dilution). 100 mg of each formulation was added to 200 mL of 0.1N HCl at 37 ^{0}C with gentle agitation using magnetic stirrer. The formulations were assessed visually for the rate of emulsification and the final appearance of the emulsion.

CLOUD POINT DETERMINATION[10]:

Cloud point temperatures (Tc) were determined by visual observation. 0.5 mL of formulation was diluted to 50 ml with distilled water in a glass beaker. The sample was heated at the rate of about 0.5^{0}C /min. A close observation was made at the appearance of the dispersion with increase in temperature. The temperature at which the dispersion became turbid was taken as Tc. After the temperature exceeds the cloud point, the sample was cooled below Tc, and then it was heated again to check the reproducibility of the measurements.

EFFECT OF DILUTION MEDIA[10]:

Dilution study was done to access the effect of dilution media on S-SNEDDS, in order to mimic physiological dilution process after oral administration. In this study the optimum formulation was subjected to various dilutions (i.e.100, 200, 1000 times) and by various diluents i.e. double distilled water, simulated gastric fluid (SGF) simulated intestinal fluid (SIF). The diluted nanoemulsions were stored for 24 h and observed visually for drug precipitation and phase separation.

IN-VITRO DRUG RELEASE STUDY[13, 14]:

The in vitro release study of SNEDDS was performed using USP XXIII type II dissolution apparatus. Each capsule was added in 900 ml of 0.1 N HCl at 37±0.5^{0}C and a paddle speed of 100 rpm. 5 mL aliquots of the samples were successively withdrawn at 10, 20, 30, 45 and 60 minutes and replaced with an equal volume of fresh

dissolution medium maintained at same temperature. The aliquot was immediately filtered, diluted suitably and determined for concentration of repaglinide by UV spectrophotometer (Shimadzu-1800, Japan) at 237 nm.

RESULT AND DISCUSSION:

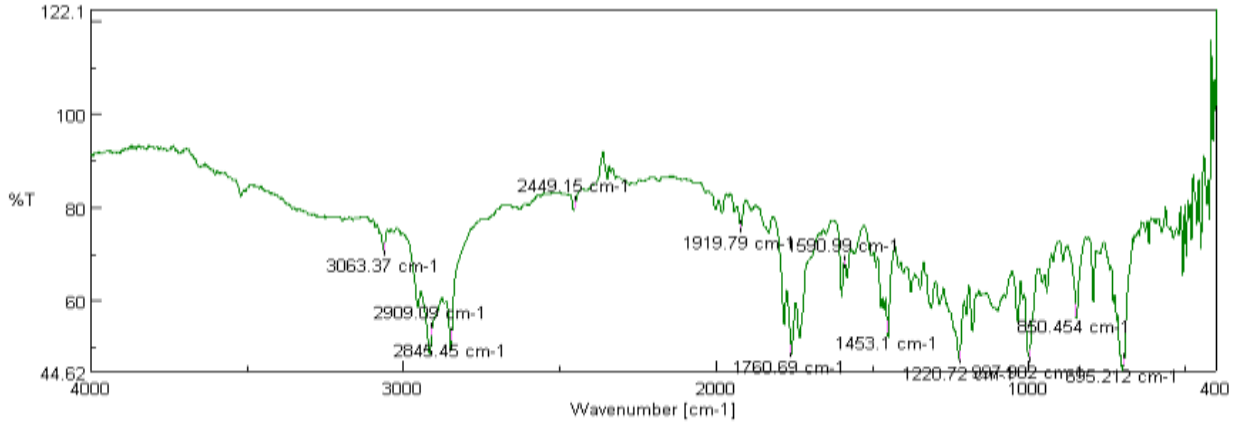

Figure 1: FTIR Spectrum of Repaglinide

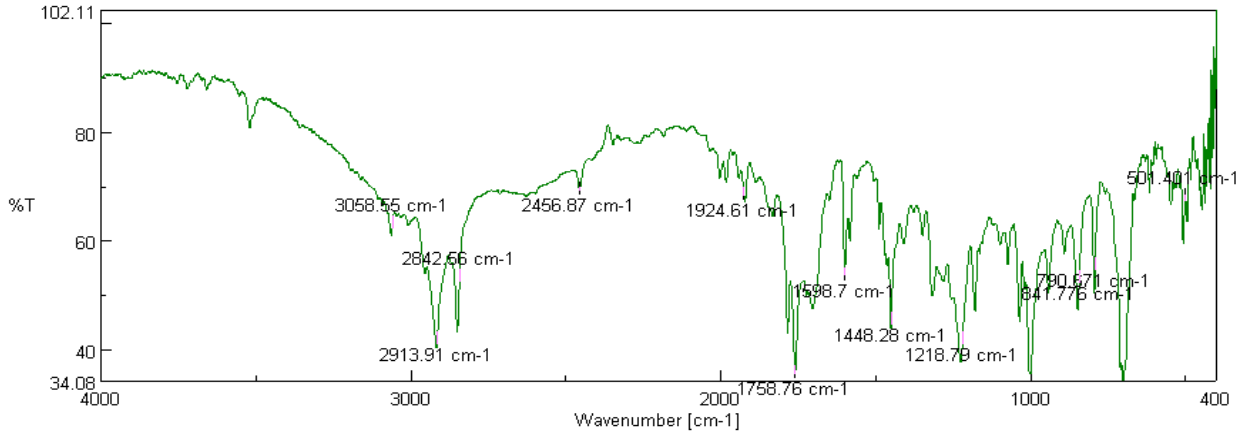

Figure 2: FTIR Spectrum of Repaglinide formulation:

COMPATIBILITY TESTING:

The FTIR spectrum of pure repaglinide and repaglinide SNEDDS formulation are shown in fig 1 and 2 respectively. The spectra revealed that there was no interaction between repaglinide and selected excipients.

FORMULATION DESIGN:

The solubility of the drug was tested in four different oily phases (Oleic Acid, Captex® 200, Capmul® MCM and Labrafill® M1944CS) that are commonly utilized in SNEDDS formulation. Results of solubility studies in oils, surfactants and co-surfactants phases are shown in Figures 3, 4 and 5 respectively. This demonstrated that solubility of the repaglinide was found to be highest in the Labrafill® M1944CS followed by Capmul® MCM. So these two oil phases were selected for preparation of SNEDDS.

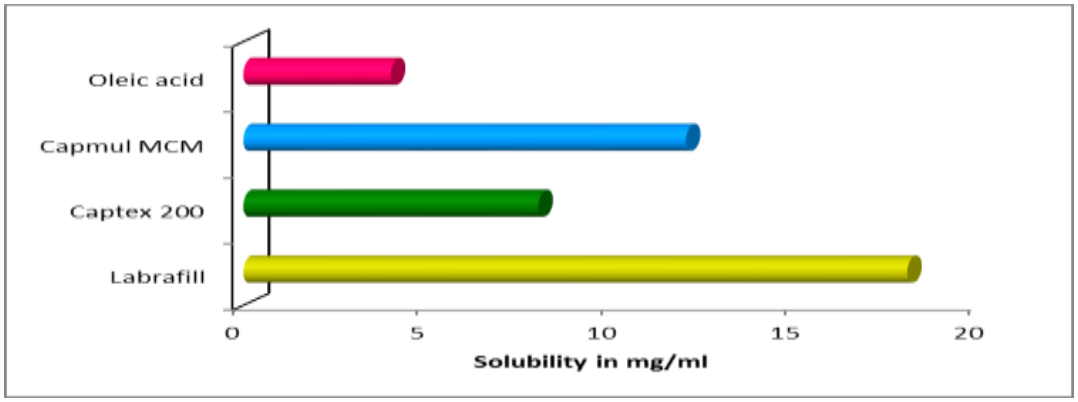

Figure 3: Solubility of repaglinide in various oils

Because of low toxic nature of non-ionic surfactants they are accepted for oral use. In this study, the four selected non-ionic surfactants (Tween® 80, Tween® 20, Cremophor® EL and Cremophor® RH40) were used to study emulsification ability of surfactant. As shown in Figure 4, drug solubility in Tween® 80 was higher than in other surfactants. Nevertheless, it exhibited the highest emulsification efficiency with all oils utilized, so it was selected for preparation of SNEDDS.

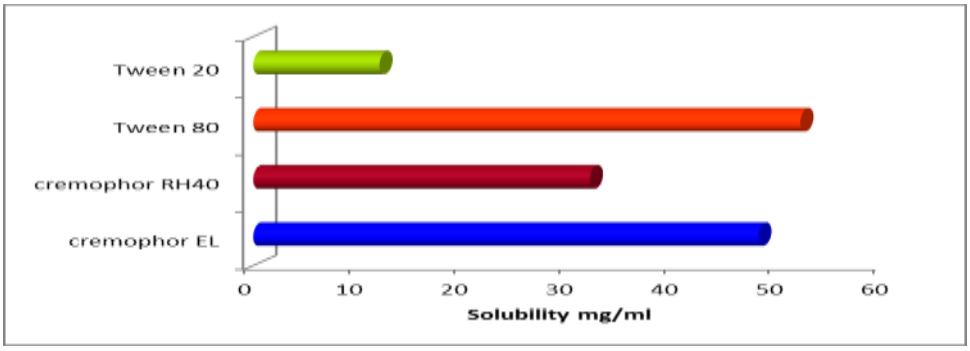

Figure 4: Solubility of repaglinide in various surfactants

Addition of a co-surfactant to SNEDDS formulation was reported to improve dispersibility and drug absorption from the formulation. In current study, four co-surfactants, namely propylene glycol (PG), polyethylene glycol (PEG), plurol oleque® and Transcutol® P were selected. The drug showed highest solubility in Transcutol®P.

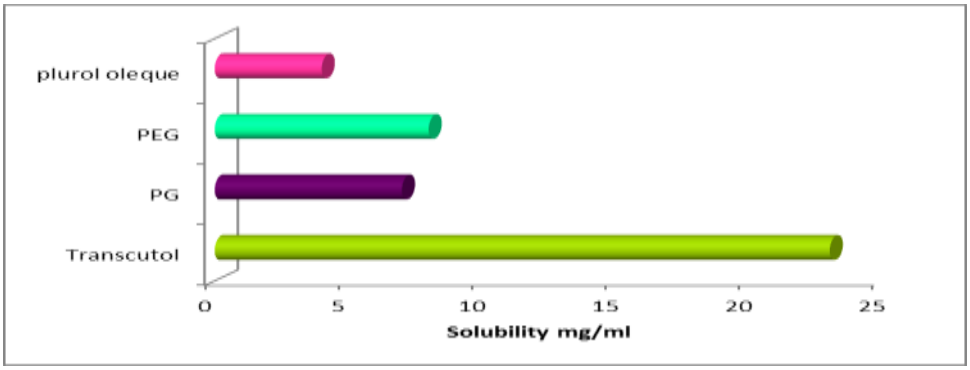

Figure 5: Solubility of repaglinide in various co-surfactants

Surfactant	% Transmittance			
	Oleic Acid	Capmul® MCM	Captex® 200	Labrafill® M1944CS
Tween® 20	39±2.31 %	67±0.37 %	45±0.21 %	67±0.09 %
Tween® 80	49±4.64 %	92±0.09 %	63±0.26 %	98±0.18 %
Cremophor® EL	67±2.52 %	93±0.17 %	65±0.08 %	96±0.1 %
Cremophor® RH40	61±3.47 %	82±0.25 %	60±0.34 %	94±0.14 %

Table 3. Emulsification study of various surfactants using different oily phases

As shown in Table 4, Capmul® MCM, Labrafill® M1944CS Transcutol® P was selected as co-surfactant to use with exhibited good emulsification with Transcutol® P with Labrafill® M1944CS and Capmul® MCM-C8 as oils and transmittance 103% and 99% respectively. Therefore Tween 80 as surfactant for optimization study.

Co-Surfactant	% Transmittance	
	Labrafill® M1944CS /Tween® 80	Capmul® MCM/ Tween® 80
PG	58±2.0 %	75±0.37 %
PEG	63±1.6 %	78±0.09 %
Plurol oleque	46±0.3 %	58±0.17 %
Transcutol® P	99±0.09 %	103±0.25 %

Table 4: Emulsification study of various co-surfactants using Tween 80 as surfactant and Labrafill and Capmul as oils phases.

Pseudo-ternary phase diagrams were constructed to identify the nanoemulsion regions and to identify the nanoemulsion regions and to optimize concentration of selected formulation variables. From phase diagrams it was observed that an increase in concentration of co-surfactant, the area of nanoemulsion was increased. The phase diagrams are shown in fig 6.

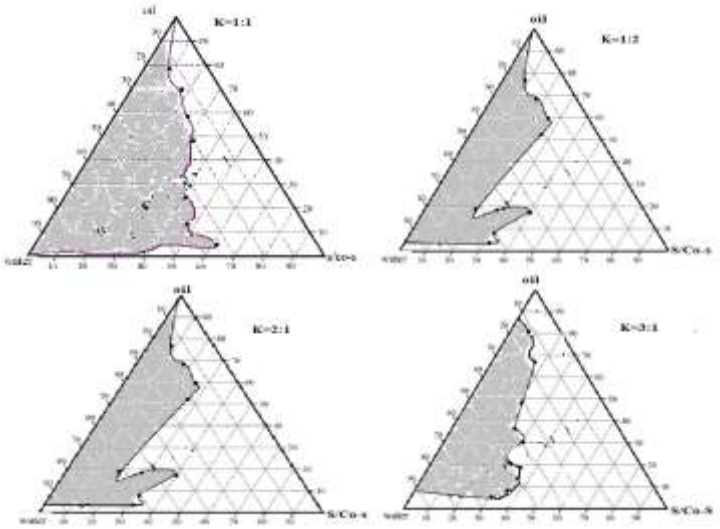

Figure 6: Ternary phase diagrams of system containing Labrafill® /Capmul® as oil, Tween 80 as surfactant and Transcutol® P as co-surfactant in different Surfactant/Co-surfactant (K) ratios.

Formulation Code	% Drug release	Globule size	Cloud Point
F1	62.65 ± 0.04	297 ± 5.9 nm	41 ^{0}C
F2	51.34 ± 0.19	121 ± 3.6 nm	45 ^{0}C
F3	68.56 ± 0.24	115 ± 4.7 nm	41 ^{0}C
F4	97.00 ± 0.29	92 ± 3.5 nm	49 ^{0}C
F5	100.05 ± 0.01	53 ± 5.4 nm	56 ^{0}C
F6	98.103 ± 0.02	85.7 ± 2.67 nm	61 ^{0}C
F7	88.07 ± 0.1	> 1 µm	63 ^{0}C
F8	37.87 ± 0.25	> 1 µm	54 ^{0}C
F9	42.83 ± 0.31	> 1 µm	41 ^{0}C
F10	49.72 ± 0.36	> 1 µm	43 ^{0}C
F11	49.30 ± 0.49	> 1 µm	41 ^{0}C

Table 5: Drug release, globule size and cloud point

OPTIMIZATION OF REPAGLINIDE SNEDDS USING D-OPTIMAL MIXTURE DESIGN:

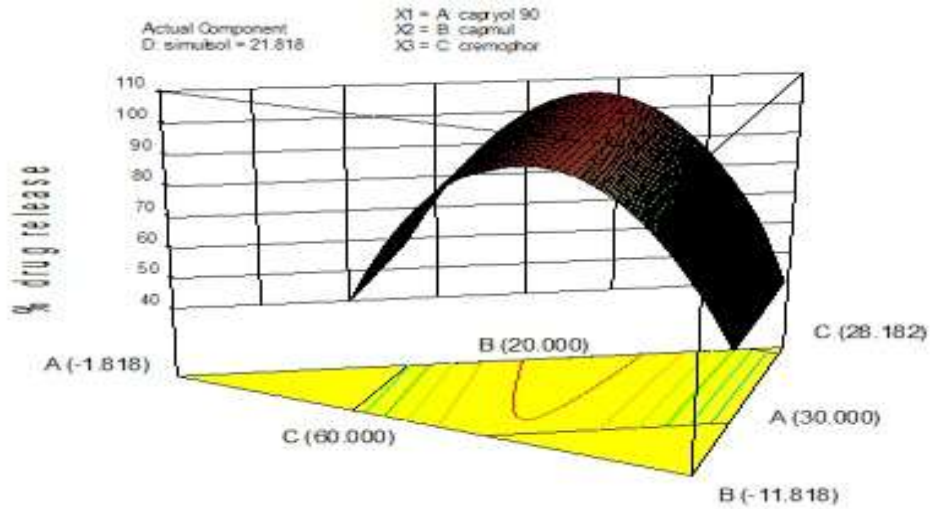

Figure 7: 3-D Response surface plot for effect of independent variables on % Drug release

Coefficient	% Drug Release (Y1)	globule size (Y3)
B1(X1)	-34.09594	+440.69399
B2(X2)	+0.45044	-74.14313
B3(X3)	-1.18958	+52.01525
B4(X4)	-1.16519	+64.99681
B12(X1X2)	+0.52040	-4.124
B13(X1X3)	+0.54464	-7.09942
B14(X1X4)	+0.53956	-6.1866
B23(X2X3)	-4.95904E-003	+0.35205
B24(X2X4)	-0.024969	+0.52420
B34(X3X4)	+5.06724E-003	-1.82227

Table 6: Coefficient for Quadratic equation for each independent variable

D-optimal mixture experimental design was applied in the present study to obtain optimal repaglinide loaded SNEDDS. Labrafill® M1944CS (X1), Capmul® MCM-C8 (X2), Tween® 80 (X3) and Transcutol® P (X4) were chosen as formulation variables and cumulative amount released after 60 min (Y1) and globule size (Y2) were selected as response variables. The responses of these formulations are summarized in Table 5.

The independent and response variables were related using polynomial equation with statistical analysis through Design-Expert® software. Quadratic model was the most suitable because its R^2 was nearer to 1. The values of the coefficients X1 and X2 are related to the effect of these variables on the response. A positive sign of coefficient indicates a synergistic effect while a negative term indicates an antagonistic effect upon the response. The larger coefficient means the independent variable has more potent influence on the response.

Model	Coefficient	% Drug Release (Y1)	Globule size (Y2)
Quadratic	SD	3.15	76.34
	R^2	0.9975	0.9970
	Adjusted R^2	0.9861	0.9837
	PRESS	10112.29	5.940E+006

Table 7: Regression results of the measured responses

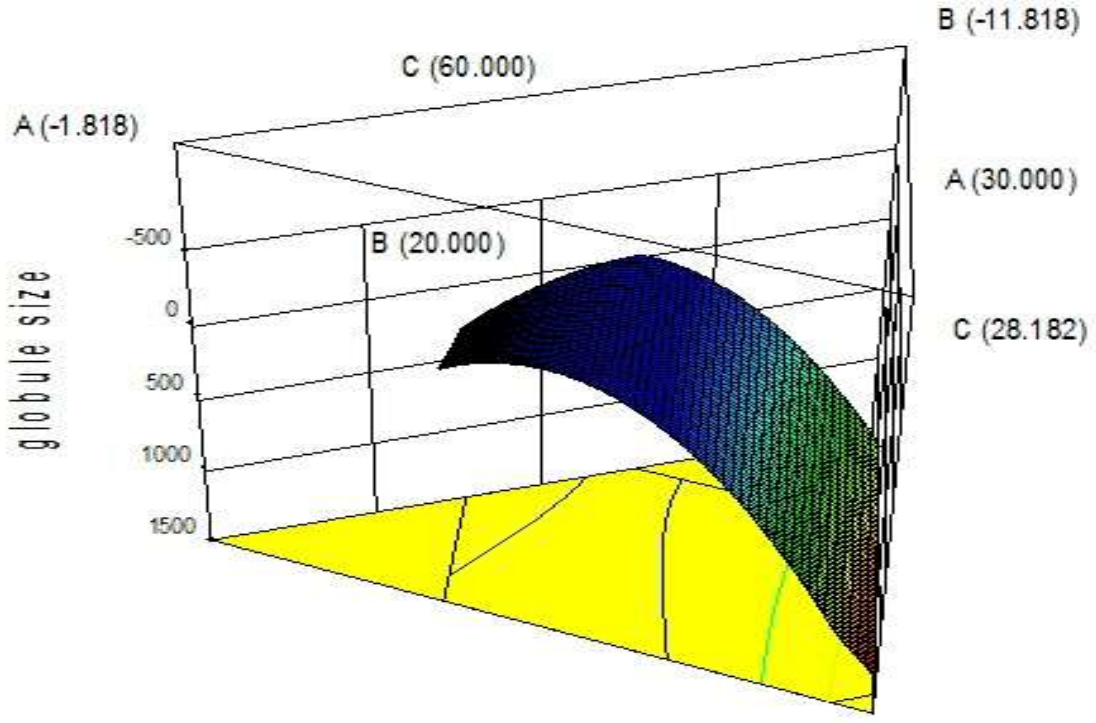

Figure 8: 3-D Response surface plot for effect of independent variables on globule size

Using D-optimal mixture design, 11 formulations of repaglinide SNEDDS were prepared and evaluated for in vitro drug release, globule size, cloud point, self-emulsification time. The results are shown in table 5. Fig 9 shows the in vitro drug release of the prepared formulations. The data obtained from in vitro drug release (response Y1) and globule size (response Y2) was analyzed using Design Expert® Software (version 8.1; Stat-Ease, Inc., Minneapolis, MN). The coefficient of quadratic equation of the independent variables and the regression results are shown in table 6 and 7 respectively.

Based on the calculated model, the response surface plots for drug release (Y1) and globule size (Y2) are shown in fig 7 and 8 respectively. As illustrated in table 8, p-value of ≤ 0.05 for all factors in analysis of variance (ANOVA) indicated significant effect of the corresponding responding factors on Y1 and Y2.

From table 5 it was revealed that formulation with lower oil level and higher surfactant level showed higher % drug release.

All the prepared formulations had shown cloud point in the range of 41 to 63 ^{0}C. The cloud point of SNEDDS should be above 37 ^{0}C which will avoid phase separation occurring in the GI tract. The cloud point of all the prepared formulations was above 37 ^{0}C therefore it was anticipated that a stable nanoemulsion could be formed at physiological temperature in vivo. Formulation F5 was considered an optimum with good results with all response variables. Formulation F5 showed 100.05 % drug release, 53 nm globule size and 13 s self emulsification time.

F5 was further subjected to effect of dilution with different media. In all cases, increased dilution and change in diluents had no effect on the appearance and stability of formed nanoemulsion of formulation F5. From these results it was indicated that formulation F5 was robust to dilution with different diluents. Thus F5 was predicted to maintain its performance in vivo.

Model	Coefficient	Y1	Y2
ANOVA	F value	88.02	74.77
	P value	0.0113	0.0133

Table 8: ANOVA results of the measured responses (Y)

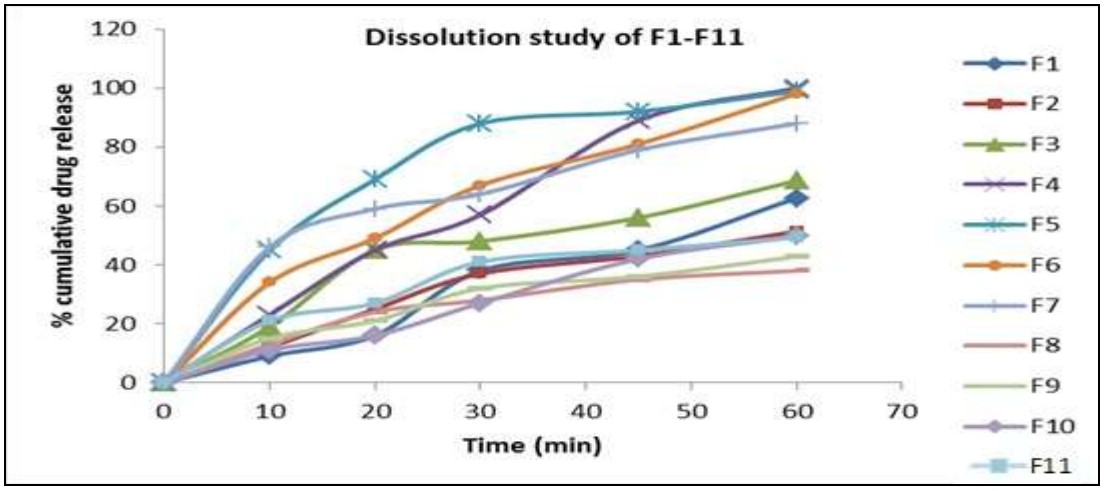

Figure 9: In-vitro drug release profile of formulations F1 to F11

CONCLUSION:

D-optimal mixture experimental design was used to optimize repaglinide SNEDDS in the present study. Eleven formulations were prepared and evaluated in vitro. Out of these F5 was found to be optimum containing 31.2 % w/w of lipid, 47 % w/w of surfactant and 21.3 % w/w of co-surfactant. The optimized formulation of repaglinide showed significant increase in dissolution rate. The significant increase in drug dissolution and solubility of repaglinide in the developed SNEDDS of repaglinide propose that the prepared system could be promising to improve oral absorption of repaglinide.

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