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Development and Evaluation of Self Micro Emulsifying Drug Delivery System of Cilnidipine

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ABSTRACT

The main objective of the current research work was development and characterization of self-micro emulsifying drug delivery system of cilnidipine which is poorly water-soluble drug. The improved solubility could offer improved dissolution as well as oral bioavailability. Component excipients were selected based on the preliminary studies, capryol 90 and triacetin (1:1) selected as an oil, tween 80 selected as surfactant, transcutol p selected as co-surfactant based on the maximum solubility and better emulsification efficiency. The ternary phase diagram was constructed to identify the optimum composition of the formulation. Simplex centroid mixture design was applied for selection of optimized batch of SMEDDS. Capryol 90 and triacetin, tween 80 and transcutol p were taken as an independent variables X1, X2 & X3 respectively, while emulsification time (Y1) and % drug release at 2 minutes (Y2) were taken as dependent variables. Optimized SMEDDS was evaluated based on % transmittance, emulsification time, globule size, PDI, % drug release, and cloud point. After that, SMEDDS were filled in capsule and short-term stability study was done and SMEDDS compared with pure drug for dissolution profile. Optimized batch containing capryol 90 and triacetin (1:1), tween 80 and transcutol p at a concentration of 10%, 67% and 23% respectively. The solubility of cilnidipine is increased by using capryol 90 and triacetin (1:1) as an oily phase. All the evaluation parameters of the optimized SMEDDS were met the acceptance criteria. Optimized batch of SMEDDS showed > 90% drug release within 2 minutes. Dissolution was improved as compared to the pure drug**.** A self-micro emulsifying drug delivery system of cilnidipine was developed successfully. Present work demonstrated for improving the dissolution of cilnidipine. This may lead to improved oral bioavailability of cilnidipine for the treatment of hypertension.

Keywords: Cilnidipine, SMEDDS, Solubility, Dissolution enhancement.

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INTRODUCTION

Hypertension (high blood pressure) is an important risk factor for the future development of cardiovascular disease. Hypertension is usually defined as a systolic pressure above 140 mm Hg and a diastolic pressure above 90 mm Hg. Patients in the high-normal range require frequent blood pressure monitoring, patients in stage 1, 2, or 3 should be under the care of a physician.[1]

It is estimated that around 30% of the population (50 million Americans) has high BP (≥140/90mm Hg). Complications occur in hypertension like myocardial infarction, hypertensive encephalopathy/malignant hypertension, etc. Primary sign of hypertension is elevated BP, abnormal heart rate or rhythm, baseline hypokalaemia, presence of protein, blood cells, and casts in the urine. Hypertension is treated by various classes of drugs like ACE Inhibitors, calcium channel blocker and diuretics etc. The drugs are most often administered by an oral route, but approximately 40% of new drug candidates have poor water solubility and the oral deliveries of such drugs is difficult because of their low bioavailability, high intra and inter subject variability, and a lack of dose proportionality. To overcome these problems, various strategies are exploited including the use of surfactants, lipids, permeation enhancers, micronization, salt formation, cyclodextrins, nanoparticles and solid dispersions. Self-micro emulsifying drug delivery system (SMEDDS) are defined as isotropic mixtures of natural or synthetic oils, solid or liquid surfactants, or one or more hydrophilic solvents and co-solvents/surfactants that have a unique ability of forming fine oil-in-water (o/w) micro emulsions upon mild agitation followed by dilution in aqueous media, such as GI fluids, these systems can form fine oil-in-water (o/w) emulsions (10–1000 nm) or micro emulsions (less than 200 nm). When compared with simple emulsions, which are sensitive and metastable dispersed forms while SMEDDS are physically and thermodynamically stable formulations that are easy to manufacture. Thus, for lipid soluble drug compounds that exhibit dissolution rate limited absorption; these systems may offer an improvement in the rate and extent of absorption and result in more reproducible blood-time profiles. [2,3]

Rational behind selecting cilnidipine is a dihydropyridine calcium channel blocker used for the treatment of hypertension. Cilnidipine is BCS class II drug, having low solubility and high permeability. Its poor solubility affects dissolution as well as an oral absorption of the drug. Self-micro emulsification can improve the solubility of the drug and hence it may also lead to improve the dissolution as well as an oral absorption of the cilnidipine. Thus, the objective of the present research work was development and characterization of self-micro emulsifying drug delivery

system of cilnidipine which is poorly water-soluble drug. The improved solubility could offer an improved dissolution as well as an oral bioavailability.[4]

MATERIALS AND METHOD

Chemicals

Cilnidipine was procured as gift sample from Pure Chem Pvt. Ltd. (Ankleshwar, India), Capryol 90 oil was purchased from Gattefosse (France), Triacetin was purchased from Orex Pharma pvt. Ltd. (Maharashtra, India), Tween-80 Surfactant was purchased from Lobachemie Pvt. Ltd., (Mumbai, India), Transcutol P Co- Surfactant was purchased from Gattefosse (France).

Methodology

Solubility study of cilnidipine in various excipients [5,6] :

Drug was solubilized in different oily phase, so the lipid vehicle which was selected should have a better solubility to the drug. The solubility of cilnidipine in various oils, surfactants and co-surfactants was showed in Figure 2. Surfactant (emulsification study). Different surfactants were screened for its emulsification ability selected in oil phase. Surfactant selection was done on the basis of % transparency and ease of emulsification.

Co-Surfactant (emulsification study). screening was done on the basis of % transparency and ease of emulsification. Mixtures of the co-surfactant, selected surfactant, and the selected oil were prepared and evaluated in similar fashion as described in the above section on surfactants.

Construction of ternary phase diagrams [7,8]:

Ternary phase diagrams representing oil: surfactant: co-surfactant excipients of the selected SMEDDS systems will be constructed. A series of self-micro emulsifying system were prepared with various weight ratios of oil, surfactant, and co-surfactant. SMEDDS with various concentration ratio of oils (5-50%), surfactant (50-95%) and co-surfactant (0-30%) was used and prepared. The oily phase was mixed with the surfactant/co-surfactant mixture and the dis-persion was homogenized in a shaking water bath 37°C for 10 minutes. From each mixture, 1mL in 50mL distilled water and mixed gently with magnetic stir bar. If clear or slight bluish micro emulsion was rapidly formed of globular size 200 nm or lower was considered in the microemulsion region of the diagram construction of ternary phase diagram without drug and with drug showed in Figure 2.

Preparation of cilnidipine SMEDDS [9,10]:

SMEDDS formulation was prepared based on its ability to form large self-emulsification region in ternary phase diagram and to obtain stable micro emulsion. Cilnidipine (10 mg) first dissolve in oil

with continuous stirring then after complete dissolution of drug, add surfactant and co-surfactant. The mixture was mixed gently by magnetic stir bar until solution becomes clear.

Optimization of SMEDDS formulation [11-14]:

To optimize the formulation and process variables, the concentration of three excipients (oil-capryol 90 and triacetin, surfactant-tween 80, and co-surfactant transcutol p) was selected as an independent variable. Emulsification times, % drug release were selected as responses. These were then optimized using a simplex centroid design. Ten trials were conducted as per the design generated using Design Expert® 11.0 trial version as listed in Table 1. The optimization of the concentration of capryol 90 and triacetin (X1) was carried out between the range of 0.10 to 0.30 %W/W, concentration of tween 80 (X2) was carried out in the range of 0.60 to 0.80%w/w and concentration of transcutol p was carried out between the range 0.10 to 0.30 %W/W. The emulsification time (sec.) (Y1) and % drug release at 2 min. (%) (Y2) were fixed as the dependent variables for the study. The analysis of variance (ANOVA) was performed to decide the right model fit. The equations for all the dependent variables were obtained. The response surface plots were generated to understand the effect of interactions of the respective dependent variable. An overlay plot was constructed to narrow down the region of the independent variables that would lead to the development of a robust product with the desired properties, viz. The measured responses have to be optimized in Design expert 11 in which response variable Y1 was (12.3) minimum and Y2 was (92.60) maximum. The optimal desirability was found 0.985.

Table 1: Details of batches taken as per simplex centroid design

Run	X1 (Capryol 90 & Triacetin) (%W/W)	X2 (Tween 80) (%W/W)	X3 (Transcutol P) (%W/W)
F1	0.10	0.80	0.10
F2	0.10	0.60	0.30
F3	0.30	0.60	0.10
F4	0.23	0.63	0.13
F5	0.13	0.63	0.23
F6	0.17	0.67	0.17
F7	0.13	0.73	0.13
F8	0.20	0.60	0.20
F9	0.20	0.70	0.10
F10	0.10	0.70	0.20

Evaluation Parameters [16-20]

% Transmittance: 1 ml SMEDDS was reconstituted with 50 ml distilled water and the resulting Micro emulsion was observed visually for any turbidity. Thereafter, % transmittance was measured at wavelength 638.2 nm using UV–Visible Spectrophotometer.

Centrifugation test:

Sample was diluted 50 times with distilled water and centrifuged at 3500 rpm on for 30 min. and then examined visually for any phase separation.

Emulsification time:

Emulsification time is the time for a pre-concentrate to form a homogeneous mixture (upon dilution) was monitored by visually observing the disappearance of SMEDDS and the final appearance of the nanoemulsion in triplicate. A dissolution apparatus was employed with 250 ml water, and with a paddle speed of 50 rpm at 37°C. The SMEDDS (1 ml) was added drop wise to the medium by a dropping pipette and the time required for the disappearance of the SMEDDS was recorded.

Determination of globule size and size distribution:

Aliquot (1 ml) of formulations, serially diluted 50-fold with purified water was employed to assess the globule size and size distribution using Malvern Zetasizer.

Cloud-point measurement:

SMEDDS were diluted with distilled water in the ratio of 1:50 placed in a water bath and its temperature was increase gradually. Cloud point was measured as the temperature at which appearance of cloudiness, both by visually and determining transmittance using UV Visible–spectrophotometer.

Robustness to Dilution:

Robustness to dilution was studied by diluting the formulations to 50, 100 and 1000 times with dissolution media (0.1 N Hydrochloric Acid). The diluted samples were stored for 24 h and observed for any sign of phase separation or precipitation. Experiments were repeated in triplicate for each formulation at room temperature.

In-vitro drug release study:

The dose equivalent to 5 mg Cilnidipine loaded SMEDDS was placed in a USP-II dissolution test apparatus. The dissolution test was performed using 900ml of 0.1 N HCl as a dissolution medium. Temperature and speed of the paddle were maintained to 37±0.5 °C and 50 rpm respectively. At predetermined time intervals (0, 2, 4, 6, 8 and 10 min) an aliquot (5ml) of the samples was collected and filtered through a membrane filter (0.45mm) at each time 5ml of fresh medium (0.1 N HCl) was added to dissolution medium. The concentration of drug was determined by using UV spectroscopy (Shimadzu, Japan) at λmax 241 nm.

Short Term Stability Study [21-22]

The optimized SMEDDS formulation was subjected to short term stability study (as per ICH guideline) was carried out under the condition 40º C ± 5º C temperature and 75% ± 5% relative

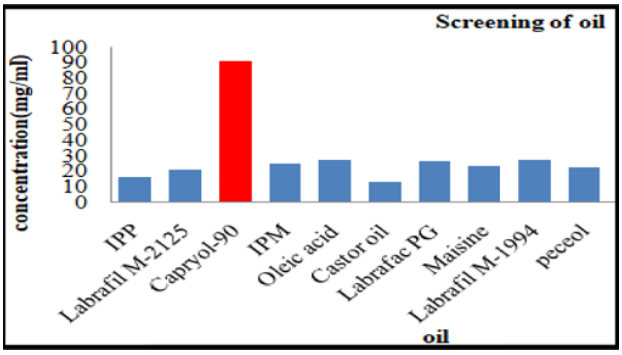
humidity in stability chamber. It was performed for 1 month. Formulation was evaluated for emulsification time and % in vitro drug release. Initial formulation was coded as A and after one month it was denoted as an A1. The % bias for emulsification and for % Drug release study was calculated.

RESULTS AND DISCUSSION

Selection of ExcipientsSolubility study of Cilnidipine in various excipients:

Drug was solubilized in different oily phase, so the lipid vehicle which was selected should have a better solubility to the drug.

Among the various oils, capryol 90 showed maximum solubilization capacity of the cilnidipine. But after the addition of aqueous media in SMEDDS microemulsion that was formed but after remained turbid in preliminary batches, so it was decided to add triacetin, drug with capryol 90 (1:1). It gave higher solubility (137.56 mg/mL) and form stable and clear microemulsion. Among all surfactant screened, cilnidipine showed maximum solubility in tween 80 (567.56 mg/mL). Among the all co-surfactant screened, cilnidipine showed maximum solubility in transcutol p (312.16 mg/mL). based on Figure 1 observation concluded that triacetin with capryol 90 (1:1) selected as an oil, while tween 80 selected as surfactant and transcutol p selected as a co-surfactant.



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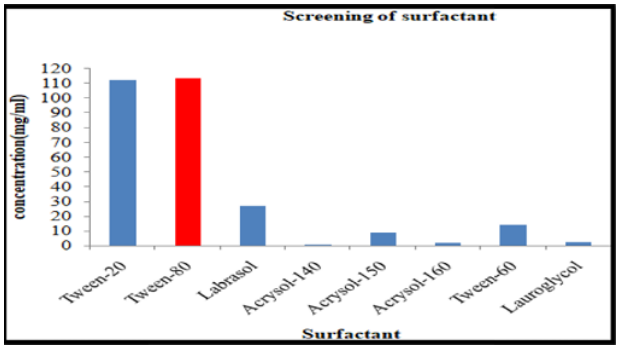

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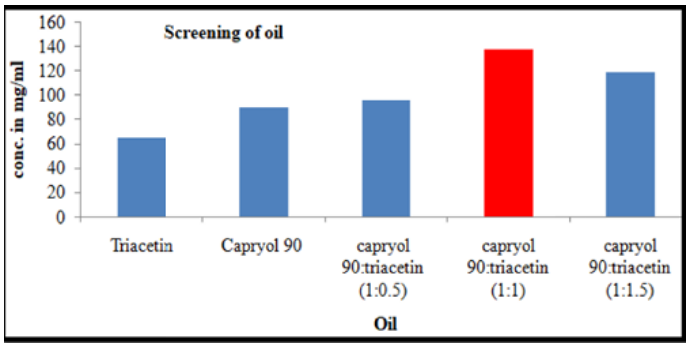

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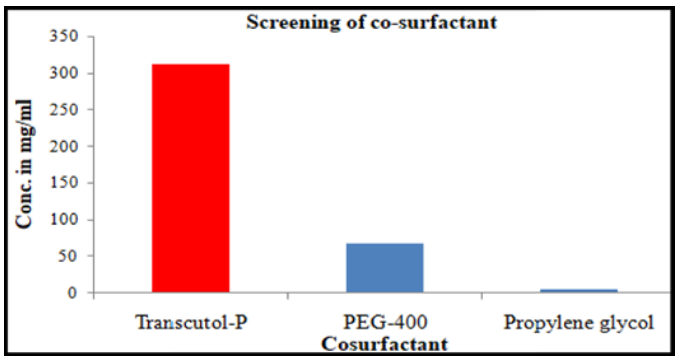


(D)

Figure 1: Graphical Representation - Solubility of cilnidipine in various oils (A), surfactants(B), co- surfactant (C), solubility studies in triacetin and capryol 90-triacetin mixture(D)

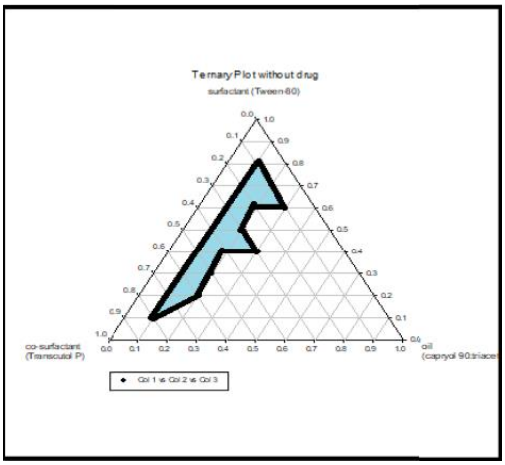
Construction of ternary phase diagram

The first step of the formulation development was to identify the self-micro emulsifying region. To identify the self-micro emulsifying region, ternary phase diagrams were prepared by using oil, surfactant, and co-surfactant, each representing the apex of the triangle. [23]

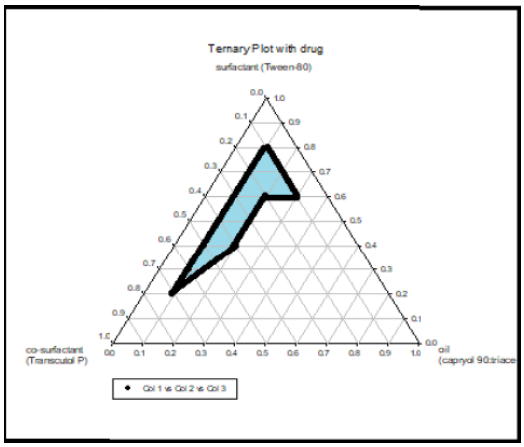
Ternary phase diagram was prepared by using Capryol 90 and Triacetin (1:1) as oily phase, Tween 80 as surfactant and Transcutol-P as co-surfactant with varying composition.

The oily phase was mixed with the surfactant/co-surfactant mixture and the dispersion was homogenized in a shaking water bath 37°C for 10 minutes. From each mixture, 0.5 gm or 1 gm were diluted with 50 ml distilled water and mixed gently with magnetic stir bar. If clear or slight bluish micro emulsion was rapidly formed of globular size 200 nm or lower was considered in the micro emulsion region of the diagram.

From result, ternary phase diagram was developed using 36 preliminary trials batches which were diluted with 50 ml distilled water. Among there 36 batches, 16 batches were found to be clear after dilution. There batches were evaluated further by addition of 10 mg of drug and then diluted up to 50 ml water to evaluate clarity of the micro emulsion.



(A)



(B)

Figure 2. Ternary phase diagram (without drug) (A), Ternary phase diagram (with drug)(B)

Experimental Protocol [24]

From preliminary studies it was concluded to apply a mixture design to optimize proper ratio of individual excipient. But here individual component cannot be taken at 0% level and 100% level. There are constraints, which impose a minimum and maximum limit on each individual excipient to study their effects. To study this type of factors in mixture design, Simplex Centroid Mixture design is best available option and we wish to obtain the best overall precision in estimating the coefficients.

As per the preliminary study, Capryol 90 and Triacetin (1:1) as oil which has maximum solubility of Cilnidipine, Tween 80 selected as a surfactant, and Transcutol P selected as co-surfactant which is selected based on its emulsifying capacity. The range fixed for Capryol 90 and Triacetin was 10 to 30% and for Tween 80 it is 60 to 80%. Transcutol P which was selected as a co-surfactant was used in the range of 10 to 30%.

Capryol 90 and Triacetin, Tween 80 and Transcutol P were selected as independent variables. The dependent variables were selected Emulsification time and % drug release at 2 min.

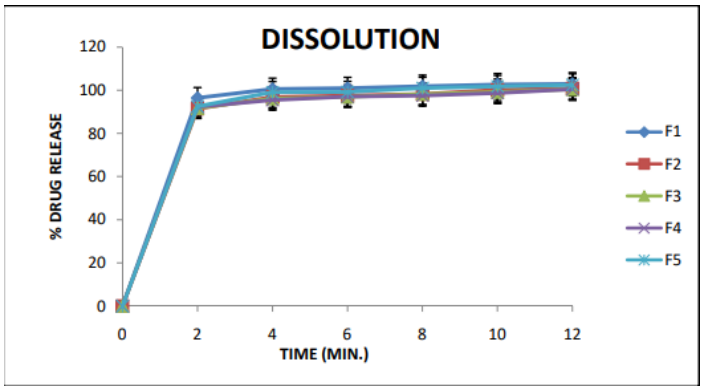
Experimental design was having 10 runs with different levels of individual mixture components. Main effects and their interaction are shown in table. Responses were subjected to regression analysis with these independent factors as linear model. For all the responses, polynomial equation was derived from multiple regression analysis.

Table 2: Results of the trials taken during the optimization studies

Batch no.	Value of Independent variables			Value of dependent variables	
	X1 Oil (%W/W)	X2 Surfactant (%W/W)	X3 Co-surfactant (%W/W)	Y1 Emulsification Time (sec.)	Y2 % drug release at 2 min. (%)
F1	0.10	0.80	0.10	18	96.5
F2	0.10	0.60	0.30	8	91.5
F3	0.30	0.60	0.10	10	91.7
F4	0.23	0.63	0.13	12	92.4
F5	0.13	0.63	0.23	11	92.6
F6	0.17	0.67	0.17	13	93.1
F7	0.13	0.73	0.13	15	95.2
F8	0.20	0.60	0.20	9	91.1
F9	0.20	0.70	0.10	15	94.6
F10	0.10	0.70	0.20	14	94.3

Dissolution profile of design batches

In vitro drug release of F1-F10 design batch of SMEDDS was studied using a USP dissolution apparatus type II at 50 rpm and maintaining temperature at 37±0.5 ^{0}C From the Figure 3 it could be concluded that there was appreciable variation in % drug release when the concentration of oil, Surfactant and co-surfactant changes from lower to higher level.



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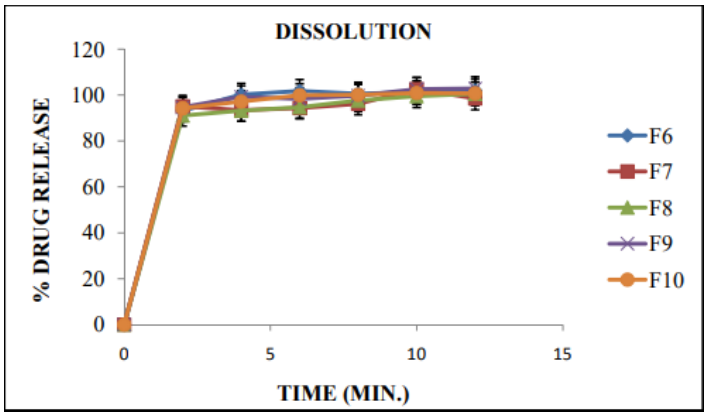


(B)

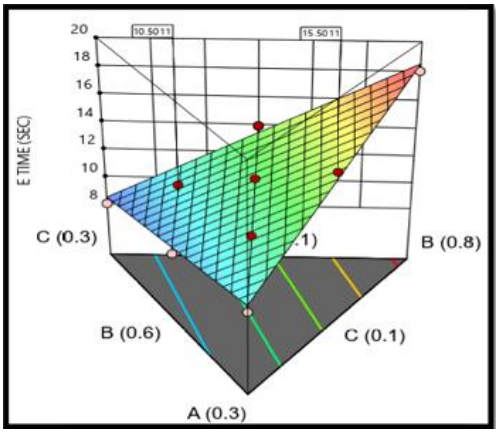
Figure 3: % drug release of design batches (A- F1 to F5),(B- F6 to F10)

Statistical analysis of design batches

The ANOVA was performed and the model was fitted for each dependent variable. The equations were constructed for each dependent variable as listed in Table 3.The 3D response surface plots to study the interaction between the independent variables to affect the dependent variables were plotted and were as shown in figure 4.

Table 3: Polynomial equations generated for dependent variables

Dependent variables	Polynomial equations	Predicted R^2
Emulsification Time (Y_1)	$-12.59X_1+27.52X_2-22.59X_3$	0.998
% Drug Release at 2 minutes(Y_2)	$76.30X_1+102.65X_2+75.50X_3$	0.999



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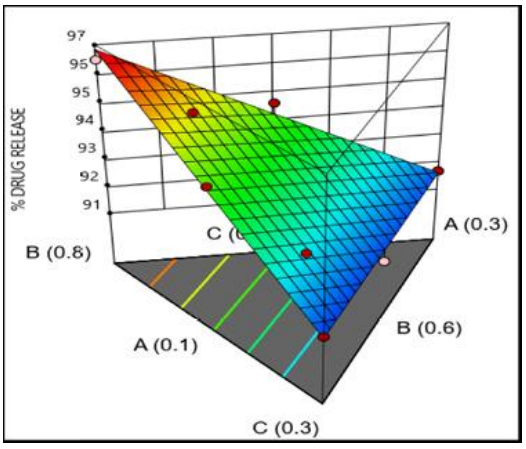


(B)

Figure 4: 3D Response surface plots for (A) Emulsification Time, (B) % Drug Release at 2 minutes.

Optimization of SMEDDS

The aim of the optimization of pharmaceutical dosage form was to determine the levels of the variable from which a robust product with high quality characteristics can be produced. An overall desirability function relies on all the investigated formulation variables used to predict the ranges of variables where the optimum formulation might occur. The desirable ranges are from zero to one (least to most desirable, respectively).[25] The measured responses have to be optimized in Design expert 11 in which response variable Y1 is minimum and Y2 maximum. The optimized batch is presented in figure 37 and optimal desirability was found 0.985.

Table 4: selection of optimized batch

Sr. no	Oil	Surfactant	Co-Surfactant	E. Time (sec.)	% Drug Release	Desirability	
1	0.100	0.670	0.230	12	93.35	0.985	Selected
2	0.120	0.666	0.214	12	93.26	0.985	
3	0.201	0.650	0.150	12	92.89	0.982	
4	0.207	0.649	0.145	12	92.86	0.981	
5	0.238	0.642	0.119	12	92.72	0.980	
6	0.262	0.638	0.100	12	92.61	0.979	

Table 5: Formula of optimized batch

Sr.no.	Components	Quantity (mg)
1	Cilnidipine	10
2	Capryol 90 and Triacetin (1:1)	10
3	Tween 80	67
4	Transcutol-P	23

Table 6: Evaluation parameter of optimized formulation

Sr.no.	Parameter	Result
1	Globule Size	4.66 nm
2	Poly Disparity Index	0.026

3	Emulsification Time	12.3 sec.
4	% Transmittance	100.1%
5	Robustness to Dilution	No precipitation
6	Centrifugation Test	No Phase Separation
7	% Drug release (2 min.)	93.60%
8	Cloud Point	75-80°c

Table 7: Observed value and predicted value along with % Bias

Responses	Predicted value	Observed value	% Bias
Emulsification time (Y1)	12	12.3	-2.43
% Drug Release at 2 min. (Y2)	93.35	93.60	-0.26

Table 8: Result of dilution study and % T of F1-F10 Design batches of SMEDDS Formulation

Batch	Dilution with distilled water			Dilution with 0.1 N HCl			% T
Code	1:50	1:100	1:250	1:50	1:100	1:250	
F1	√	√	√	√	√	√	98.23
F2	√	√	√	√	√	√	100.1
F3	√	√	√	√	√	√	99.41
F4	√	√	√	√	√	√	100.1
F5	√	√	√	√	√	√	99.32
F6	√	√	√	√	√	√	100.1
F7	√	√	√	√	√	√	98.69
F8	√	√	√	√	√	√	99.10
F9	√	√	√	√	√	√	100.2
F10	√	√	√	√	√	√	100.4

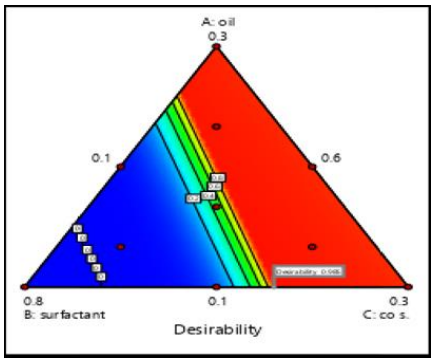


Figure 5: Desirability profile for response optimization (contour plot)

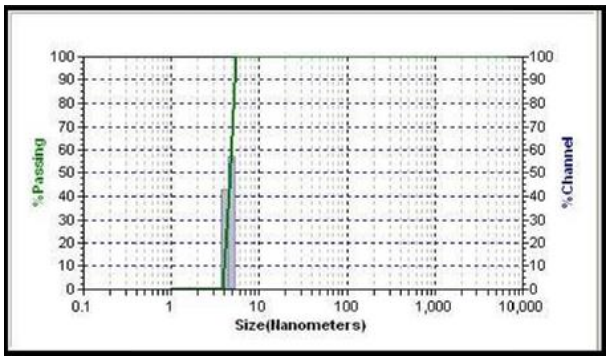
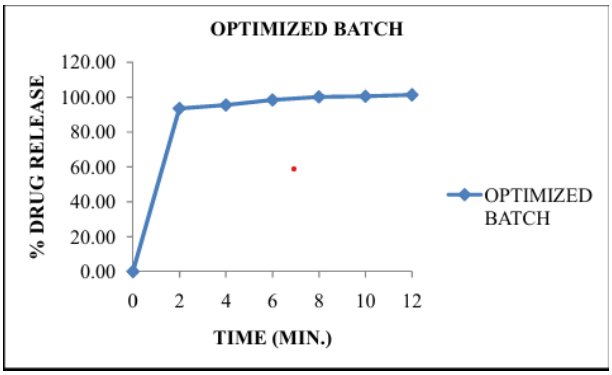


Figure 6: Globule size of optimized batch



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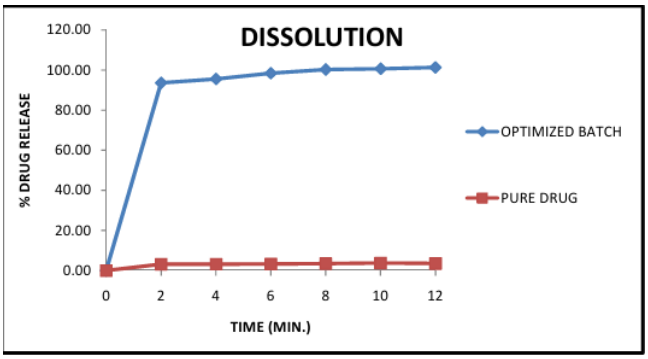

(B)

Figure 7: Drug release of Optimized Batch (A), Comparison of Drug release of SMEDDS and Pure Cilnidipine (B)

Short Term Stability Study

No significance change after short term accelerated stability study was found in % drug release study as shown in table 40. % Bias for emulsification time was -1.6 % and % drug release at 2 min was 0.580 %. Both value lies within range is indicator of high stability of prepared SMEDDS Formulation.

Table 9: Optimized batch SMEDDS formulation evaluation before and after Short term stability study

Responses	Before stability	After stability	% Bias
Emulsification time (Y1)	12.3	12.5	-1.6
% Drug Release at 2 min. (Y2)	93.60	93.06	0.580

CONCLUSION

In present investigation Self-micro emulsifying drug delivery system (SMEDDS) of Cilnidipine was developed for enhancement of solubility and dissolution rate. During preliminary investigation, Capryol 90 and Triacetin (1:1), Tween 80 and Transcutol-P were selected based on its solubility and emulsification efficacy respectively. Ternary phase diagrams were prepared with and without Cilnidipine with different ratio of above components. It was found that there was

reduce in micro emulsification area with and without drug. Most of formulations showed % Transmittance above 90 %, globule size below 10 nm and > 90 % CPR within 2 min. Simplex Centroid Design was used to quantify the effect of independent variables on dependent variables. The optimized formulation prepared having values of dependent variables like 12.3 sec emulsification time, 4.66 nm average globule size, 93.60 % drug release at 2 minutes.

In vitro drug release of optimized formulation of SMEDDS was found significantly higher than pure drug. Short term accelerated stability study shows no significance change in Emulsification time and % drug release, which was confirmed by % Bias. Emulsification time % bias was -1.6 and for % drug release it was found to be 0.580. It could be concluded that the novel SMEDDS of Cilnidipine shows improvement in solubility and rate of dissolution of the drug.

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