ORIGINAL ARTICLE

Mixed solvency concept in reducing surfactant concentration of self-emulsifying drug delivery systems of candesartan cilexetil using D-optimal mixture design

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The objective of this present study was to explore the utility of "mixed solvency" concept to enhance the solubility of poorly-water soluble drug, candesartan cilexetil (CC) in modified solubilizer system. The objective of this paper is to reduce the surfactant concentration traditionally involved in the formulation of self-emulsifying drug delivery systems (SEDDS) by proposing an alternate system of solubilizer to provide novel surfactant/cosurfactant system, to aid traditionally involved components in the formulation of SEDDS. The present study showed that "mixed solvency" concept was successfully employed in solubility enhancement of CC in (Transcutol P: B_3Mix [1:1]) up to 303 mg/g of blend. Present study demonstrated the promising use of "mixed solvency" concept in solubility enhancement of poorly-water soluble drugs and tool to reduce the net surfactant concentration employed in designing of SEDDS.

Key words: *Candesartan cilexetil, drug delivery system, hydrotropy, mixed solvency, mixture design, surfactant, self-emulsifying, self-emulsifying drug delivery systems*

INTRODUCTION

Now-a-days, an increasing number of new chemical entities and many existing drugs exhibit low solubility in water, which may lead to poor oral absorption, high intra- and inter-subject variability and lack of dose proportionality. Thus, for such compounds of Biopharmaceutics Classification System (BCS) II type, the absorption rate and degree from the gastrointestinal tract (GIT) are usually controlled and limited by dissolution process. To overcome the problem, various formulation strategies have been adopted including the use of cyclodextrins, nanoparticles, solid dispersions, and permeation enhancers. In recent years, much attention has been paid to self-emulsifying drug delivery systems (SEDDS), which have shown lots of reasonable successes in improving oral bioavailability of poorly soluble drugs.[1-4] SEDDS are usually composed of a mixture of oil and surfactant or cosurfactant and are capable of forming fine oil-in-water emulsions upon gentle agitation provided by the GIT motion. After oral administration, SEDDS can maintain the poorly soluble drugs dissolved in the fine oil droplets when transiting through the GIT.[5,6]

Poor aqueous solubility is a common concern in the formulation of pharmaceutical dosage forms. There are several established methods for increasing the equilibrium solubility of non-polar drugs in aqueous vehicles. Cosolvency, the addition of water miscible solvents to an aqueous system, is one of the oldest, most powerful, and most popular of these. Cosolvents are organic liquids that are substantially miscible with water and find a high degree of utility in the design of many types of liquid formulations.[7-9]

In some cases, the use of appropriate cosolvent can increase the aqueous solubility of a drug by several orders of magnitude. In other cases, the solubilizing effect is much smaller or even negligible and in still

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other cases the addition of a cosolvent will reduce the solubility of a solute in an aqueous vehicle.[10,11]

Maheshwari proposed the concept of mixed solvency. she is of the opinion that all substances whether liquids, solids or gases have solubilizing power and water soluble substances may enhance the solubility of poorly water soluble drugs. It is the increase in solubility of poorly soluble drugs by the addition of more than one solubilizing agent. Use of these agents in combination may enhance the solubility of poorly soluble drugs by miraculous synergistic effect in addition to the additive effect.[12,13]

Melted polyethylene glycol PEG-4000, PEG-6000, PEG-8000 (temperature less than 100°C) and melted urea (M.P.: 132-135°C) dissolves diclofenac sodium (M.P.: 283°C). This shows that melted PEGs and urea act as solvent for diclofenac sodium. Melted ibuprofen (M.P.: 78°C) dissolves diclofenac sodium (M.P.: 283°C), salicylic acid (M.P.: 159°C) and niacinamide (M.P.: 132°C), which again shows that melted ibuprofen acts as solvent for diclofenac sodium, salicylic acid and niacinamide, respectively. Additives may either increase or decrease the solubility of a solute in a given solvent. The effect of an additive depends very much on the influence; it has on the structure of water or its ability to compete with the solvent water molecules.[14-20]

In the present study, an attempt was made to enhance the solubility of candesartan cilexetil (CC) by formulating it as SEDDS incorporating modified system of solubilizer along with the conventional components used, for filling into hard gelatin capsules. CC is an esterified prodrug of candesartan, a non-peptide angiotensin II type 1 receptor antagonist used in the treatment of hypertension. Based on its solubility across physiologically relevant pH conditions and absorption characteristics, CC is classified in the Biopharmaceutics Classification System as a class II drug. Low solubility of CC across the physiological pH range is reported to result in incomplete absorption from the gastrointestinal tract and hence is reported to have an oral bioavailability of about 15%. CC is a highly lipophilic compound and has good solubility in tri- and diglyceride oils. These factors, therefore, may contribute toward absorption via the lymphatic route.

MATERIALS AND METHODS

Materials

CC was a generous gift from Dr. Reddy's Laboratories Ltd., Hyderabad, India, and medium chain triglyceride oil (Capryol-90), macrogolglyceride (Labrasol), tween 80, labrafac cc, Lauroglycol 90, transcutol were a generous gift from Gattefosse (Mumbai), India. Capmul PG-8 (propylene glycol monocaprylate) was a generous gift from Abitech Coroporation, USA. Acrysol K-140 was a generous gift from Corel Pharma Chem, Ahmedabad, India. Cremophor RH 40, Cremophor EL and Lutrol-F68 were a generous gift from BASF (Mumbai), India. L-Camphor, Vanillin, Menthol were a generous gift from Shagun Pharmaceuticals (Indore), India. Soybean oil, castor oil, olive oil, and oleic acid were purchased from local market. Acetonitrile was of high performance liquid chromatography (HPLC) grade purchased from SRL Chemicals, India. Water, double distilled in all glass still, was used in all experiments. All other chemicals used were of analytical grade. All chemicals were used as received.

Methods

Solubility studies

The objective of solubility studies is to determine the solubilization capacity for the drug in given vehicles. Vehicles, which show the highest solubility, are then used for formulation of SEDDS. The solubility of CC in various vehicles, i.e., oils (Capryol-90, soybean oil, corn oil, capmul PG-8, olive oil, oleic acid, castor oil, labrafac PG), surfactants (Acrysol, Cremophor EL, Labrasol, tween 80, tween 20, span 20) and cosurfactants (PEG 400, Lauroglycol 90, transcutol, lutrol F-68,) was determined initially.

The solubility of CC was also determined in modified solubilizer systems (Camphor 30% in ethanol (wt/wt), Camphor 60% in ethanol (wt/wt), Menthol 30% in ethanol (wt/wt), Menthol 60% in ethanol (wt/wt), Vanillin 30% in ethanol (wt/wt), Vanillin 60% in ethanol (wt/wt), Lutrol F-68 30% in ethanol (wt/wt), lutrol F-68 60% in ethanol (wt/wt), and combinations of thereof viz. C/V 20/20, C/V 20/40, C/V 40/20, V/L 20/20, V/L 20/40, V/L 40/20, C/L 20/20, C/L 20/40, C/L 40/20, C/V/L 10/10/10, C/V/L 20/20/20 where C denotes Camphor, V denotes Vanillin, L denotes Lutrol F-68, and digits denotes the percentage of components (Camphor, Vanillin, Lutrol-F68) in solution in ethanol (wt/wt). For example, C/V/L 20/20/20 denotes 20% Camphor, 20% Vanillin, and 20% Lutrol F-68 in ethanol (wt/wt).

A total of 5 mL of each of the selected vehicles were added to each cap vial containing an excess of CC and the mixture was gently heated at 45-60°C in a water bath under continuous stirring using the vortex mixer to facilitate drug solubilization. Vials were kept at ambient temperature for 72 h to attain equilibrium. After reaching equilibrium, each vial was centrifuged at 2000 rpm for 20 min, and excess insoluble CC was discarded by filtration using the syringe filter (Millipore Millex-HN Nylon 0.45 µm). Aliquots of supernatant were diluted with methanol and the concentration of solubilized CC dissolved in various vehicles was quantified by HPLC method at 254 nm.

HPLC analysis

The HPLC analysis was carried out using the Merck Lachrome high performance liquid chromatography system (Lachrome, Merck Hitachi). Chromatographic separation was accomplished using an octadecylsilyl column (Lichrosphere® 100), C_{18}, 250 mm × 4.6 mm, 5 µm stainless steel column. The mobile

phase consisted of a mixture of buffer (0.02 M monobasic potassium phosphate), acetonitrile, and triethylamine in the ratio of 40:60:0.2, with pH adjusted to 6.0 using the phosphoric acid. The mobile phase was pumped isocratically at a flow rate of 2.0 ml/min during analysis. The amount of drug dissolved at each sampling point was estimated using UV wavelength of 254 nm.

Screening of surfactants for emulsifying ability

Emulsification ability of various surfactants was screened. Briefly, 300 mg of surfactant was added to 300 mg of the selected oily phase. The mixture was gently heated at 45-60°C for homogenization. The isotropic mixture, 50 mg, was accurately weighed and diluted with double distilled water to 50 ml to yield fine emulsion. The ease of formation of emulsion was monitored by noting the number of volumetric flask inversions required to give uniform emulsion. The resulting emulsions were allow to stand for 2 h and their transmittance was assessed at 633 nm by UV-160A double beam spectrophotometer (Shimadzu, Japan) using the double distilled water as blank

Screening of cosurfactants

The turbidimetric method was used to assess the relative efficacy of the cosurfactants to improve the nano-emulsification ability of the surfactant and also to select best cosurfactant from the large pool of cosurfactant available for design of formulation. Acrysol®, 200 mg was mixed with 100 mg of cosurfactant. Capryol90 (CAE), 300 mg, was added to this mixture and the mixture was homogenized with the aid of the gentle heat (45-60°C).The isotropic mixture, 50 mg, was accurately weighed and diluted to 50 ml with double distilled water to yield fine emulsion. The ease of formation of emulsions was noted by noting the number of flask inversions required to give uniform emulsion. The resulting emulsions were observed visually for the relative turbidity. The emulsions were allowed to stand for 2 h and their transmittance was measured at 638.2 nm by UV-160A double beam spectrophotometer (Shimadzu, Japan) using the double distilled water as blank. As the ratio of cosurfactants to surfactants is the same, the turbidity of resulting nanoemulsions will help in assessing the relative efficacy of the cosurfactants to improve the nanoemulsification ability of surfactants.

Pseudoternary phase diagram studies

In order to identify self-emulsifying regions as well as suitable components, pseudo-ternary phase diagrams containing oil, surfactant, cosurfactant, and water were constructed by aqueous titration method. On the basis of solubility studies of CC in different vehicles, Capryol-90 were selected as the oil phase, On the basis of solubility and emulsifying ability Acrysol was selected as surfactant. The sizes of the nanoemulsion region in the diagrams were compared. Briefly, various self-emulsifying formulations were prepared by mixing oil and surfactant/cosurfactant mixture in varying volume ratio from 9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8, and 1:9, in separate glass vials. Cosurfactant system ratio containing Transcutol *P* and B_3Mix was maintained constant at 1:1, 1:2, and 2:1. Mixtures were homogenized with the aid of gentle heat (45-60°C). Pseudo-ternary phase diagrams were developed using aqueous titration method and were mapped with the help of Sigma Plot software (version 11.0). Slow titration with an aqueous phase was carried out to each weight ratio of oil and S_{mix} and visual observation was carried out for transparent and easily flowable nano-emulsions. The physical state of the nanoemulsion was marked on a pseudo-three-component phase diagram with one axis representing aqueous phase, the other representing oil and the third representing a mixture of surfactant and cosurfactant at fixed weight ratios (S_{mix} ratio). The phase diagrams are shown in Figures 1-5.

Construction of ternary phase diagrams

A series of self-emulsifying formulations were prepared with varying concentrations of oil, surfactant, and cosurfactant.

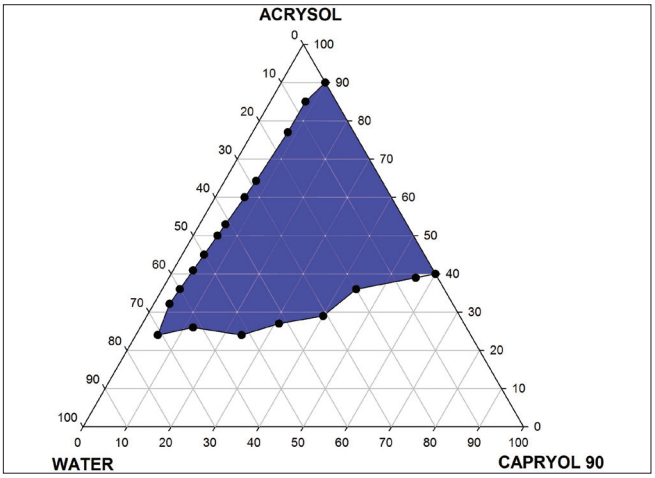

Figure 1: Pseudoternary phase diagram for Capryol-90 as oil phase, Acrysol® as surfactant and water

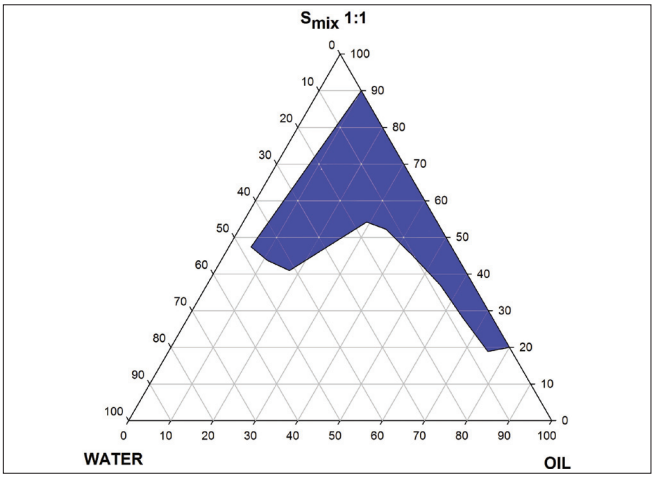

Figure 2: Pseudoternary phase diagram for Capryol-90 as oil phase, Acrysol®: TB_3Mix (1:1) as S_{mix} and water

Concentration of capryol-90 was varied from 10% to 55% (w/w) as an oil phase, Acrysol® from 30% to 75% (w/w) as surfactant and Transcutol P: B_3Mix (1:1) (TB_3Mix) from 0% to 40% (w/w) as cosurfactant at an interval of 5%. Total of the oil, surfactant, and cosurfactant always added up to 100% in each mixture. Each formulation was homogenized with the help of gentle heat up to 45-60°C. Accurately weighed 50 mg of each of 47 mixtures was then emulsified to 50 ml with distilled water separately, under the conditions of gentle shaking and the resultant emulsion was allowed to stand undisturbed for 15 min for equilibration. The selection of emulsification range was carried out on the visual clearance and % transmittance. Only those compositions having % transmittance more than 70% and clear appearance were considered desirable and were used in plotting the ternary phase diagram. Ternary phase diagrams were plotted using the Sigma Plot software. Desirable self-emulsifying region and concentration range of each component were identified as shaded are from the phase diagram shown in Figure 6.

Computer-aided optimization of SEDDS formulation using mixture D-optimal design

The pre-optimization studies concluded the ranges of oil (Capryol 90), surfactant (Acrysol®) and cosurfactant (TB_3Mix) were 10-30%, 40-70% and 10-40% respectively. These concentrations were subjected to optimization using Design Expert software (Version 8.0.3) of Stat-Ease, Inc. Minneapolis, USA. A variation in concentration of any of these components causes a change in the droplet size, isotropicity, polydispersity index, drug release as well as other properties of the formulation. Thus, concentration of oil, surfactant and cosurfactant were chosen as the independent variables or factors. The lower and upper limits of each factor were selected on the basis of the pre-optimization studies as well as compatibility of possible combinations by software.[21] The total amount of all the three components in a formulation always summed up to 100%. The variables along with their ranges are recorded in Table 1.

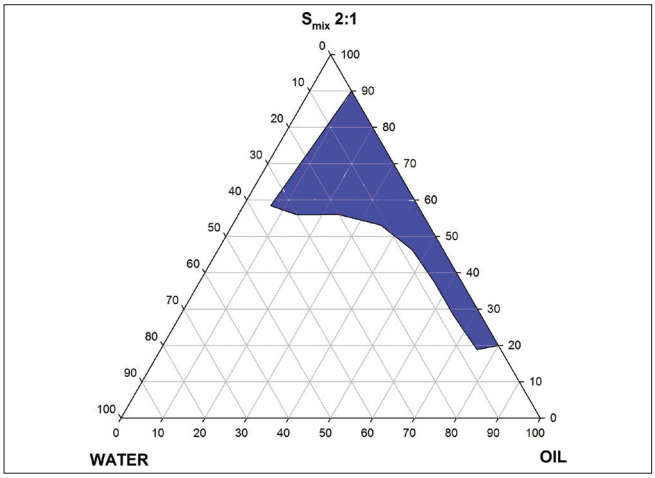

Figure 3: Pseudoternary phase diagram for Capryol-90 as oil phase, Acrysol®: TB_3Mix (2:1) as S_{mix} and water

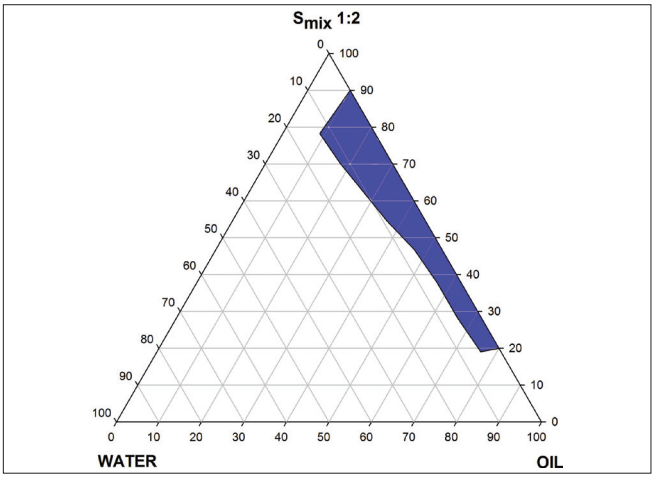

Figure 4: Pseudoternary phase diagram for Capryol-90 as oil phase, Acrysol®: TB_3Mix (1:2) as S_{mix} and water

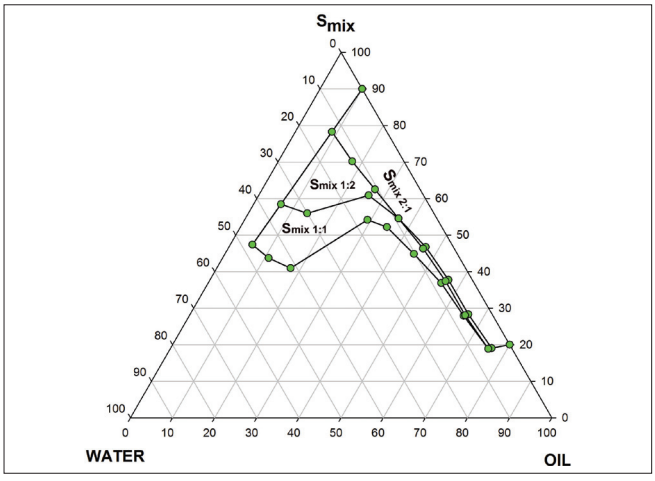

Figure 5: Comparative pseudoternary phase diagram for Capryol-90 as oil phase, Acrysol®: TB_3Mix as S_{mix} and water

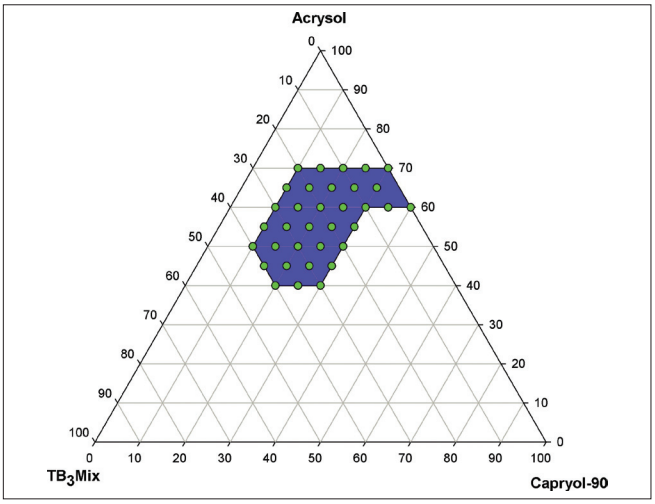

Figure 6: Ternary phase diagram for Capryol-90, Acrysol® and TB_3Mix

Constraint Applied for Independent Variables
Amount of oil + Amount of surfactant + Amount of cosurfactant = 100%
Amount of surfactant ≥ Amount of cosurfactant.

Four responses include cumulative % drug release in 30 min (Y1) Average droplet size (nm) (Y2), polydispersity index (Y3), and turbidity (Y4) since they are generally regarded as significant factors for assessing the qualities of SEDDS. A two-factor, two levels D-Optimal Mixture Design was undertaken to investigate the main effects and the interactions of the two factors on the four responses. the design consist of 16 runs viz. Six model formulations, five runs to estimate lack of fit, and five replicate runs. The purpose of replication was to estimate experimental error and increase the precision. The independent and dependent variables are shown in Table 1, and the experimental runs with observed responses are shown in Table 2. Based on the experimental design, the factor combinations yielded different responses.

The results obtained were statistically analyzed for response variables by using Design expert software (8.0.3 version) of Stat-Ease, Inc. Minneapolis, USA.

The software generated 16 optimization batches according to the constraint applied to the system during computer aided optimization. The composition of 16 software generated batches for optimization with the amount of ingredients involved provided in columns Factor-1, Factor-2 and Factor-3 respectively of Table 2. The generated 16 optimization batches further analyzed according to known reported methods of analysis with modifications (if any) and generated scientific data is provided in columns Response-1 to Response-4 of Table 2. The generated data further feed into the software and mathematical models were applied, which in the form of mathematical polynomial equation depict the relationship between the response variable and independent variable. The optimization batches were selected on the basis of desirability function. Those formulations having desirability factor near 1.0 were selected.

Table 1: Independent and dependent variables with their ranges for optimization of SEDDS formulation

Variable	Unit	Type	Desired target		
			Lower	Upper	Goal
Independent variables					
Amount of oil	%	Numeric	10	30	-
Amount of surfactant	%	Numeric	35	60	-
Amount of cosurfactant	%	Numeric	10	45	-
Dependent variables					
Cumulative % drug release in 30 min	%	Numeric	55.80	94.41	Maximize
Average particle size	nm	Numeric	24.66	187.00	Target to 75
Polydispersity index	-	Numeric	0.133	0.416	Minimum
Turbidity	-	Numeric	0	1	Minimum

SEDDS: Self-emulsifying drug delivery systems

Table 2: Composition and evaluation of optimization batches of SEDDS formulation

Run no.	Formulation batch code	Factor-1 Amount of oil (%) (wt/wt)	Factor-2 Amount of surfactant (%) (wt/wt)	Factor-3 Amount of cosurfactant (%) (wt/wt)	Response-1 Release in 30 min (%)	Response-2 Average droplet size (nm)	Response-3 Polydispersity index	Response-4 Turbidity*
1	CCRUN 1	10	60	30	84.41	25.31	0.221	0
2	CCRUN 2	20	40	40	71.19	59.00	0.362	0
3	CCRUN 3	20	50	30	62.87	38.41	0.147	0
4	CCRUN 4	10	45	45	78.84	96.70	0.221	0
5	CCRUN 5	20	60	20	64.50	134.00	0.183	1
6	CCRUN 6	30	60	10	55.80	182.00	0.176	1
7	CCRUN 7	15	51.25	33.75	70.68	65.88	0.182	0
8	CCRUN 8	25	55	20	62.00	165.00	0.291	1
9	CCRUN 9	20	45	35	69.00	137.00	0.269	1
10	CCRUN 10	10	45	45	81.90	99.80	0.227	0
11	CCRUN 11	30	47.5	22.5	70.32	71.23	0.327	0
12	CCRUN 12	30	35	35	75.85	48.31	0.219	0
13	CCRUN 13	30	47.5	22.5	72.54	73.62	0.416	0
14	CCRUN 14	30	60	10	57.92	187.00	0.133	1
15	CCRUN 15	30	35	35	77.2	48.25	0.212	0
16	CCRUN 16	10	60	30	82.96	24.66	0.227	0

*Turbidity, 0: Clear emulsion; 1: Turbid emulsion; CCRUN: Batch code; SEDDS: Self-emulsifying drug delivery systems

Table 3: Statistical summary for the response variable

Response variable	Model	*F* value	Df	*P* value Prob>F	Adjusted R-square	Predicted R-square	Adequate precision
Y1	Quadratic	42.91	5	0.0001	0.9332	0.8921	6.248
Y2	Quadratic	7.66	5	0.0034	0.6895	0.6023	11.184
Y3	Cubic	4.64	9	0.0376	0.6862	0.9705	8.820
Y4	Quadratic	5.12	5	0.0137	0.5789	0.4749	7.463

The statistical summary of response variables is summarized in Table 3. The mathematical relationships in the form of polynomial equations for the measured responses are listed in Table 4.

PREPARATION AND CHARACTERIZATION OF OPTIMIZED BATCHES OF CC SEDDS

Preparation of optimized batches of CC SEDDS

After applying mathematical model to the 16 formulations with feed data generated during experimental analysis, the software predicted the optimized batches, which yet to be analyzed. The obtained optimized batches with respective ingredients are listed in Table 5. The optimized formulations obtained by the Design-Expert software Table 5, were prepared by spontaneous emulsification method. All the three components of the system were accurately weighed in the required amounts in glass vials. They were homogenized by gentle heating up to 45-60°C. The mixtures were then stirred using the vortex stirrer for 5 min for proper mixing of the components. 16 mg of the drug was added to each formulation and mixed using vortex stirrer for 10 min for proper solubilization of drug and development of a homogeneous formulation.

Formulation containing 16 mg of the drug was finally filled in size "2" capsule with the help of a micropipette. The capsule shell was then sealed by applying 1% gelatin solution and subsequently 70% w/v solution of alcohol on the shell joint and cooling.

Characterization and validation of predicted and observed responses obtained for CC SEDDS

Visual observation

A visual test to assess the self-emulsification properties was modified and adopted in the present study. In this method, a pre-determined weight of formulation (50 mg) was introduced into 500 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 as "good" when droplets spread easily in water and formed a fine transparent emulsion, and it was rated "bad" when there was milky or no emulsion formation with immediate coalescence of oil droplets, especially when stirring was stopped. All the trials were carried out in triplicate, with similar observations being made between repeats.

Table 4: Mathematical relationship for measured responses as polynomial equation

Cumulative % drug release in 30 min (Y1)	=	+7.24431*oil +1.18051*surfactant +0.34100*cosurfactant −0.12168*oil*surfactant −0.07951*oil*cosurfactant +0.01482*surfactant*cosurfactant
Average droplet size (nm) (Y2)	=	+7.24431*oil +1.18051*surfactant +0.34100*cosurfactant −0.12168*oil*surfactant −0.07951*oil*cosurfactant +0.01482*surfactant*cosurfactant
Polydispersity index (Y3)	=	−0.04192*oil +0.00512*surfactant +0.28316*cosurfactant +0.00160*oil*surfactant −0.006050*oil*cosurfactant −0.00587*surfactant*cosurfactant +0.00009*oil*surfactant*cosurfactant +0.00004*oil*surfactant* (oil-surfactant) −0.00002*oil*cosurfactant* (oil-cosurfactant) +0.00005*surfactant*cosurfacta nt* (surfactant-cosurfactant)
Turbidity (Y4)	=	−0.30455*oil +0.03350*surfactant +0.07390*cosurfactant +0.00440*oil*surfactant +0.00390*oil*cosurfactant −0.00276*surfactant*cosurfactant

Table 5: Composition of optimized SEDDS formulations of candesartan cilexetil

Ingredients of SEDDS	Formulation batch code			
	FCC-1	FCC-2	FCC-3	FCC-4
Amount of Capryol-90 (mg)	38.7	37.4	45.0	25.8
Amount of Acrysol® (mg)	55.6	63.7	68.7	68.0
Amount of Transcutol P (mg)	27.8	24.4	18.2	28.1
Amount of Camphor (mg)	5.6	4.9	3.6	5.6
Amount of Vanillin (mg)	5.6	4.9	3.6	5.6
Amount of Lutrol F-68 (mg)	5.6	4.9	3.6	5.6
Amount of ethanol (mg)	11.1	9.8	7.3	11.3

SEDDS: Self-emulsifying drug delivery systems, FCC: Final formulation batch code

Determination of droplet size and zeta-potential

To investigate the globule size of resultant emulsion, fifty mg of the formulations was diluted to 50 ml with distilled water and

was allowed to equilibrate for 15 min. Droplet size, distribution and zeta potential of the resulting emulsion was then measured by laser particle size analyzer (Malvern Zetasizer Nano S, Malvern Co., UK). The detection range was from 2 nm to 5000 nm.

In vitro release studies

An *in vitro* drug release study for the optimized formulations was performed using the USP paddle apparatus. The dissolution media used for study is recommended by USFDA, comprising 900 ml of 0.35% polysorbate 20 in 0.05 M phosphate buffer of pH 6.5 at 50 rpm (paddle rotation). A 166 mg aliquot of the formulation (equivalent to 16 mg of CC with 10.7% drug loading in 150 mg formulation blend) in prefilled capsule shell was placed in dissolution media and temperature was maintained at 37°C ± 0.5°C. Placebo formulations were also tested to check interference, if any. Samples were collected periodically and replaced with fresh dissolution medium. Samples after filtration through syringe filter (Millipore Millex-HN, Nylon 0.45 µm) were analyzed by HPLC method at 254 nm for CC content. 100 µl samples were drawn out at the pre-determined intervals, and the same volume of fresh dissolution medium was replenished. The release of CC from SMEDDS formulation was compared with the marketed tablet of CC containing the similar labeled dose of the drug. A sample (20 µl) was injected into HPLC.

RESULTS AND DISCUSSION

The drug CC was selected as poorly water soluble drug to demonstrate the utility of mixed solvency concept to enhance the solubility of hydrophobic molecules. The research paper is also illustrating the successful implementation of computer aided optimization methods in the formulation of SEDDS to minimize errors and improve the degree of authentication and validity of adopted scientific procedures.

The solubility of CC in different vehicles was determined as listed in Table 6. Ingredients with higher solubility for CC were selected to formulate SEDDS. Pre-optimization studies involves the preparation of pseudoternary phase diagram and Ternary phase diagrams to assess the self-emulsifying potential of various ingredients as well as mixtures, finally to decide the concentration range of phases required to formulate SEDDS.

Optimization batches involved the three independent factors to form oily phase, surfactant and modified solubilizer system or cosolvent. Capryol-90 was selected as oily phase, Acrysol was selected as Surfactant phase, whereas mixture of Transcutol-P, Camphor, Vanillin and Lutrol F-68 (TB_3Mix) were selected as alternate solubilizing system to replace cosurfactant/cosolvent phase of traditionally known methods to prepare SEDDS.

Optimization batches were evaluated and generated evaluation data were subject to Design Expert software to predict optimized batches. The data feed into the software is enlisted in Table 2 and predicted optimized batches enlisted in Table 5.

Table 6: Solubility of candesartan cilexetil in different vehicles and % transmittance in selected vehicles

Vehicle	Solubility (mg/gm)	% transmittance	Vehicle	Solubility (mg/gm)	% transmittance
Oils			Transcutol P	176.83±2.28	76.2
Capryol-90	21.31±3.26	-	Menthol 60%**	44.60±1.31	12.7
Capmul	7.19±1.19	-	Camphor 60%**	253.47±2.20	70.2
Castor oil	3.8±0.81	-	Vanillin 60%**	183.47±0.95	29.3
Labrafac PG	1.63±0.44	-	Lutrol F-68 60%**	59.22±0.27	43.8
Corn oil	1.38±0.81	-	C/V/L 20/20/20 (B_3)**	303.79±2.24	72.8
Olive oil	1.18±0.27	-	TB_3Mix**	282.81±6.73	78.3
Oleic acid	0.66±0.05	-	Camphor 30%**	145.26±1.20	-
Soyabean oil	0.32±0.02	-	Menthol 30%**	30.98±0.18	-
Surfactants			Vanillin 30%**	121.97±0.86	-
Labrasol	146.07±3.81	86.9	Lutrol F-68 30%**	33.34±0.18	-
Tween 80	241.80±9.40	24.6	C/V 20/20**	193.32±2.65	-
Tween 20	217.84±5.85	19.1	C/V 20/40**	219.18±1.70	-
Span 20	21.93±1.48	29.9	C/V 40/20**	265.34±1.71	-
Cremophor EL	103.80±1.99	78.5	V/L 20/20**	107.79±1.86	-
Acrysol®	114.29±4.32	93.7	V/L 20/40**	98.93±1.40	-
Cosurfactant/modified solubilizers			V/L 40/20**	137.55±3.48	-
Lauroglycol 90	80.51±2.38	-	C/L 20/20**	134.53±3.27	-
PEG 400	103.26±3.37	-	C/L 20/40**	118.10±1.09	-
Propylene glycol	89.51±4.32	-	C/L 40/20**	214.59±4.96	-
Ethanol	4.96±2.78	-	C/V/L 10/10/10**	210.65±1.39	-

**Solution of cosurfactant (s) in ethanol (wt/wt), C: Camphor, V: Vanillin, L: Lutrol F-68, PG: (Propylene glycol), EL: (Cremophor EL), PEG: (Polyethylene glycol), C/V: (Camphor Vanillin ratio), V/L: (Vanillin Lutrol F-68 ratio). Digits shows the % of component in solution (wt/wt), B3=20% Camphor+20% Vanillin+20% Lutrol F-68 in ethanol (wt/wt); TB_3Mix=Transcutol P+B_3 (1:1)

Table 7: Characterization of optimized SEDDS formulations (*n*=3)

Batch code	Average % transmittance	Droplet size (nm)	% Drug release in 30 min	Polydispersity index
FCC-1	98.3	109±16.8	72.44±4.28	0.292
FCC-2	94.2	97±26.1	74.42±2.53	0.269
FCC-3	95.9	157±22.4	73.87±7.42	0.147
FCC-4	97.2	93±33.8	78.82±9.31	0.164

SEDDS: Self-emulsifying drug delivery systems, FCC: Formulation batch codes

The optimized batches predicted by software were further analyzed to validate the conformity of scientific data in the form of observed values. The predicted and observed values for analyzed optimized batches are enlisted in Tables 7 and 8.

The formation clear emulsion on addition with aqueous phase with low polydispersity index indicates the spontaneous formation of SEDDS. The obtained emulsions were visually clear and not shown any sign of precipitation, coagulation or phase inversion when kept aside for at least 6 h.

The droplet size lies in the range of 80-160 nm not only confirms the closeness of observed values with predicted ones, but also infers the higher bioavailability of formed formulation due to its nano range globules size.

The drug release was found near 80% during first 30 min indicates the formulation with rapid drug release and infers higher bioavailability, which also confirms the potential application of SEDDS.

The surfactant concentration of Acrysol (surfactant) involved in the formulation of SEDDS was in the range of 32% to 45%, which is very less than the traditionally used level of surfactant (usually > 60% surfactant) that clearly indicates the potential of alternate solubilizing cosolvent mixture as a principle outcome of mix solvency to the concept in the formulation of SEDDS. Further, the level/concentration of other ingredients involved in the formulation of SEDDS lies under permitted amount according to different regulatory bodies, in fact the concentration of ingredients were very low than the permitted values under texts.

CONCLUSION

The present paper was successful in achieving the goal of reducing surfactant concentration involved in formulation of SEDDS of CC by implementation of principle of mix solvency. The improved self-emulsifying formulation formed due to enhance solubilizing effect of alternate cosolvent system by application of mix solvency principle. Traditionally, the solubility load for the formulation of SEDDS lies in oil as well as surfactant phases. However by mix solvency concept it was successfully tested that solubility can be balanced by alternate approach of modification of cosurfactant or cosolvent mixtures. The research paper also illustrates the implementation of computer aided optimization to minimize the time, error and cost involved in research procedures for better formulation development.

Table 8: Validation of optimized SEDDS formulations by predicted and observed average values

Response	Results	Formulation batch code			
		FCC-1	FCC-2	FCC-3	FCC-4
Cumulative % drug release in 30 min	Predicted	71.20	68.94	71.21	69.93
	Observed	72.44	74.42	73.87	78.82
Average droplet size (nm)	Predicted	74.99	76.58	69.66	89.27
	Observed	109	97	157	93
Polydispersity index	Predicted	0.311	0.254	0.345	0.230
	Observed	0.292	0.269	0.147	0.164
Turbidity	Predicted	0.268	0.240	0.001	0.300
	Observed	0	0	0	0

SEDDS: Self-emulsifying drug delivery systems, FCC: Formulation batch codes

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