RESEARCH PAPER

Development And In Vitro Of Characterization Novel Selfmicroemulsifying Drug Delivery System Of Low Solubility Drug Cinnarizine By Improved Bioavailability

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ABSTRACT
Objective: The objective of this study is to create a self-microemulsifying drug delivery system (SMEDDS) that will increase the solubility and bioavailability of a Biopharmaceutical Classification System -II (BCS-II) drug. Cinnarizine (CEN) is derivative of piperazine antihistamine drug with a low solubility and bioavailability. It was intended to improve the solubility and oral bioavailability of cinnarizine by creating a selfmicroemulsifying drug delivery system (SMEDDS) .
Methodology: The solubility of cinnarizine was tested with a various of oils, surfactants, and cosurfactants. On the basis of capacity to emulsify oils, surfactants were further screened. Campul MCM, Tween 80 and gelucire 41/14 was chosen as the oil, surfactant and co-surfactant in SMEDDS formulation. The microemulsion area was identified by plotting pseudoternary phase diagrams with water. Robustness to dilution, emulsification time, phase separation, droplet size, zeta potential and other factors were assessed for the prepared SMEDDS formulations.
Results: The formulation F-1 to F-3 of cinnarizine are containing campul MCM, Tween 80 and gelucire 44/14 was converted into SMEDDS in different ratio of oil and surfactant cosurfactant mixture. The formulation has globules size range 95.70 to 101.21nm, zeta potential -23.2 to -28.6mV. The vitro dissolution profile was studied in 0.1 N HCl and phosphate buffer (pH 6.8) 95.27 to 89.32%. SMEDDS with S/CoS ratio (2:1) and S/CoS oil ratio (9:1) showed the highest drug release and thermodynamically stable
Conclusion: Selfmicroemulsifying formulation of cinnarizine was successfully developed improved solubility and dissolution in comparison to pure drug, thus can serve as potential alternative to existing oral formulations..
Keywords: Solubility, Bioavailability, Dissolution, Globule size and Zeta potential.
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INTRODUCTION

In pharmacy, solubility is a basic characteristic that has a big influence on drug formulation solubility and bioavailability. The degree and rate at which a drug enters systemic circulation or its bioavailability are influenced by its solubility [1]. Low solubility drugs dissolve too slowly to be efficiently absorbed, which frequently results in low bioavailability. Pharmaceutical scientists therefore frequently focus on increasing the rate at which poorly soluble drug dissolve in order to improve solubility and bioavailability [2]. Drugs are divided into four groups by the BCS classification according to their solubility and permeability. The proper formulation techniques and regulatory requirements for bioequivalence studies are determined in part by this classification. Because Class-II and Class-IV drugs are poorly soluble, effective formulations frequently call for solubility enhancement techniques [3]. The advantage of lipid-based drug delivery systems is that they can present the drug, lipid, surfactant, cosolvents and stable liquid solutions excipients with a broad range of physicochemical characteristics [4]. Lipid-based drug delivery systems (LBDDS) are a sophisticated formulation technique that is frequently employed in pharmaceutical industrial to improve the solubility, bioavailability and therapeutic efficacy water insoluble drug. Lipids serve as the primary component of LBDDS which improves absorption permeability and solubility of drug especially those in Class-II and class-IV of the BCS. [5,6]. Lipid-based formulations known as self-microemulsifying drug delivery systems (SMEDDS) are intended to improve the solubility and bioavailability of drug that are not very soluble in water. These systems create isotropic mixtures of oil, surfactants and co-surfactants that spontaneously emulsify to create fine oil-in-water microemulsions with droplet sizes that are usually range between 10 and 100 nm. when they come into contact with gastrointestinal fluids. [7,8] SMEDDS create a microemulsion when taken orally by combining with gastrointestinal fluids. By increasing the transport of lipophilic drugs across the intestinal membrane and improving their dissolution. These smallest droplets

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frequently circulate in first-pass metabolism through lymphatic absorption [9].

MATERIALS AND METHODS

Materials

Cinnarizine was purchased from quantum Inc. scientific supplier Lucknow, UP. Cotton seed oil, sunflower oil and soybean oil were supplied by Bright Labs Hyderabad. Campul MCM (glyceryl caprylate/caprate), Tween -80, Tween -20 and Polyethylene glycol 400 were purchased from S.D. fine chemicals Mumbai, India. Labrasol, Gelucire 44/14 were purchased from Gattefosse India Private Limited, Mumbai, India. Propylene glycol and ethanol were obtained from the local suppliers. All other chemicals used for analytical grade.

Methods

Solubility Studies

Cinnarizine (CNZ) saturation solubility was evaluated in different oils (soya oil, cotton seed oil, sunflower oil, campul MCM) surfactants (Tween 80, tween 20, Labrasol) and cosurfactants (Gelucire 44/14, polyethyleneglycol-400 polyethylene glycol). An excessive amount of CNZ was used in this study then added to 5 ml of each of vehicle in volumetric flasks and mixed using a vortex mixer **for 5 min** to facilitate drug solubilization. The mixture was then kept at 37°C±0.5°C temperature for 48 hrs. to attain equilibrium. The equilibrium sample was centrifuged at 5000 rpm for 15 min to using a **bench-top centrifuge fitted with a fixed-angle rotor** to remove the undissolved drug which was then filtered and filtrate was suitably diluted with methanol and quantified by UV spectroscopy (Shimadzu UV-1700) at 253.5 nm. **All sample preparation and analysis steps were carried out under light-protected conditions to prevent photodegradation of cinnarizine. [10].**

Pseudoternary Phase Diagram Construction

Oil, water and surfactant/cosurfactant (S/CoS) pseudoternary phase diagrams were created by the water titration method. For each phase diagram at a specific ratio of S/CoS (1:1, 2:1, 3:1 and 4:1 wt./wt.). The ratio of mixture of oil and S/CoS (1:9, 2:8 3:7, 4:6, 5:5 6:4, 7:3, 8:2 9:1). The mixtures of oil and S/CoS at certain weight ratios were diluted with water in a dropwise manner then transparent and homogenous was formed by vortexing for 5 minutes. After that each mixture was examined visually to determine its flowability and phase clarity. Based on the weight measurements, the water concentration at which the transitions from turbidity to transparency and transparency to turbidity took place was determined. Then using the S/CoS mixing ratio and the chosen oil value, the boundaries of the microemulsion domain that matched were established. Drug-enriched oil was used as the hydrophobic component in phase diagrams made with the drug present to determine how the drug's addition impacted the microemulsion boundary. The Tri plot software was used to create phase diagrams [11,12,13&14].

Preparation of SMEDDS Formulations

The solubility study and pseudoternary phase diagram served as the basic for the formulation development of SMEDDS. Capmul MCM was used as oil, Tween 80 as surfactant and gelucire 44/14 as the cosurfactant to create a number of SMEDDS. A precisely weighed amount of drug was dissolved in the measured volume of oil with continuous stirring on magnetic stirrer. In another beaker ratio of mixture of surfactant and co-surfactant were combined. Until the drug was fully dissolved, the oil phase was added to the Smix while being continuously stirred. The mixture was stored at room temperature for further use.

Evaluation and Characterization of SMEDDS

Self-emulsification and Precipitation assessment

Visual assessment was used to evaluate the self-emulsifying qualities of SMEDDS formulations. The preconcentrate (SMEDDS) was added dropwise to 250 ml of distilled water for visual evaluation. The contents were gently stirred magnetically at 100 rpm while the beaker was kept at 37°C±5°C. The different compositions were categorized on speed of emulsification, appearance and disperbility of the resultant emulsion (Table-1) [15].

Precipitation was measured by visual inspection of the resulting emulsion after 24 hours. These were then classified as clear (transparent or transparent with bluish tinge), nonclear (turbid), stable (no precipitation at the end of 24 hours), or unstable (showing precipitation within 24 hours). (Table-2) [16].

Table-1 Visual assessment of criteria for SMEDDS

Grade	Self-emulsification time	Appearance	Dispersibility
I	Less than 1min.	Clear or slightly bluish	Rapid emulsification
II	Less than 2min.	Slightly less clear, bluish white	Rapid emulsification
III	Less than 3 min.	Bright white, similar in appearance to milk	Rapid emulsification
IV	More than 3 min.	Dull, greyish white emulsion, slightly oily appearance	Slow to emulsify
V	More than 3 min.	Large oil droplets present on the surface	Poor minimal emulsification

Table-2 Dispersibility test and optical clarity of criteria for SMEDDS

Grade	Result
A	The microemulsion appears clear or bluish and forms quickly (within one minute).
B	Rapidly forming emulsion with a bluish white appearance, and slightly less clear than A.

C	Emulsification in 2 min and producing a fine milky emulsion
D	Emulsification after 2 min resulting in dull, greyish white and slightly oily appearance.
E	Emulsion with minimal emulsification resulting in large oil globules.

Emulsion droplet size analysis

100 microliters of each SMEDDS formulation were diluted with distilled water in 250 ml beaker with gently stirred a glass rod. After that the resulting emulsion was put through a particle size analysis measurement range of 0.01 to 3500 um using Malvern Mastersizer equipment. Using the volume size distribution and the particle size was calculated. Every study was conducted three times and the results showed that the measurements agreed well [17&18].

Drug loading efficiency

Drug loading efficiency measurement by taking a 50 mg equivalent of SMEDDS formulation in methanol was added to bring the volume up to 100 ml and the proper dilution. The resulting solution was examined using a UV Spectrophotometer at 253.5 nm. The drug loading efficiency was determined by the following formula [19].

Drug Loading Efficiency (DLE) %=

(Amount of drug recovered/Amount of drug added) ×100

Dispersibility test and optical clarity

The USP dissolution apparatus II was used to conduct the test. 500 ml of 0.1 N HCl was placed in a dissolution vessel with 1 ml of SMEDDS formulation temperature at 37 ± 0.5°C and 50 rpm. The dispersions were graded as follows In order to measure optical clarity, the dispersion produced after dispersibility test was measured for percent transmittance at 600 nm for optical clarity. The formulation with visual grading and percent transmittance 100% were selected for further studies [20&21].

Measurement of Zeta potential and polydispersity index

The zeta potential measurement by the diluted SMEDDS formulations using a Nano Zeta sizer (Horiba Instruments, Japan). The SMEDDS were diluted with distilled water at a 1:2500 (v/v) ratio and using a magnetic stirrer for one minute. For every SMEDDS the zeta potential was measurement. The same instrument was used for assessing PDI which indicates the broadness of the size distribution of globules and surface charge (zeta potential) of the formulated SMEDDS [22&23].

Robustness to dilution

The formulation was diluted with 100 times volumes of different dissolution media in order to examine robustness to dilution namely 0.1N HCl and phosphate buffer (pH 6.8). After being stored for 12 hours. The diluted microemulsions were checked for indications of drug precipitation or phase separation [24].

In vitro drug release studies

The dose equivalent to 25 mg cinnarizine loaded SMEDDS was put into a USP-II dissolution test apparatus. A dissolution medium of 900 mL of 0.1 N HCl was used for the dissolution test, temperature and speed of the paddle were maintained to 37±0.5°C and 50 rpm respectively. 5 ml of fresh medium (0.1 N HCl) was added to the dissolution medium at pre-arranged intervals and an aliquot (5 ml) of the samples was taken and filtered through a membrane filter (0.45 mm) each time. The concentration of drug was determined by using UV spectroscopy (Shimadzu, Japan) at λmax 253.5 nm. The medium was changed to buffer pH 1.2 for determination of the in vitro dissolution of plain cinnarizine. The dissolution studies were performed in other media (buffer 6.8) to examine the effect of pH on drug release [25,26&27].

Study of thermodynamic stability

The formulation was subjected to both low and high levels of thermal and mechanical stress in this examination and the effects on the SMEDDS formulation's capacity for self-emulsification and clarity were noted. The test was carried out in two parts.

(a) Alternate cycle of heating (40°C) and cooling (4°C)

The formulations are stored at each of these temperatures alternating between 4°C and 40°C for a minimum of 48 hours for six cycles. Changes in dispersibility, self-emulsification time and optical clarity were noted along with any instability in the formulation. Centrifugation tests were conducted only on stable formulations.

(b) Centrifugation

The SMEDDS formulation was centrifuged for 30 minutes at 2000-3000 rpm and the stability of the mixture was assessed by measuring changes in dispersibility, self-emulsification time and optical clarity. The formulations which were thermodynamically stable were only taken for further study [28].

RESULT AND DISCUSSION

Solubility studies

The results of a study on the solubility of CNZ in different oils, surfactants and cosurfactants are presented in (Table-3). Solubility studies of drug in oil indicated that it was maximum soluble in Capmul MCM, Tween 80 and gelucire 44/14 and hence these excipients were short listed for the preparation of SMEDDS as oil, surfactant and cosurfactant respectively. Solubility studies were performed to identify suitable oil, surfactants, and cosurfactants for the development of SMEDDS of cinnarizine. Because an important consideration when formulating a selfmicroemulsifying formulation is avoiding precipitation of the drug on dilution (Figure-1).

Table-3 Solubility of cinnarizine in different oils, surfactants and cosurfactants

Components		Solubility (mg/ml)
Oils	Campul MCM Soyabean oil Cotton seed oil Sunflower oil	98.37 27.56 30.27 21.98
Surfactants	Tween 80 Tween 20 Labrasol	68.79 57.21 45.69
Cosurfactants	Gelucire 44/14	49.83 47.35

	PEG 400 Propylene glycol	24.86

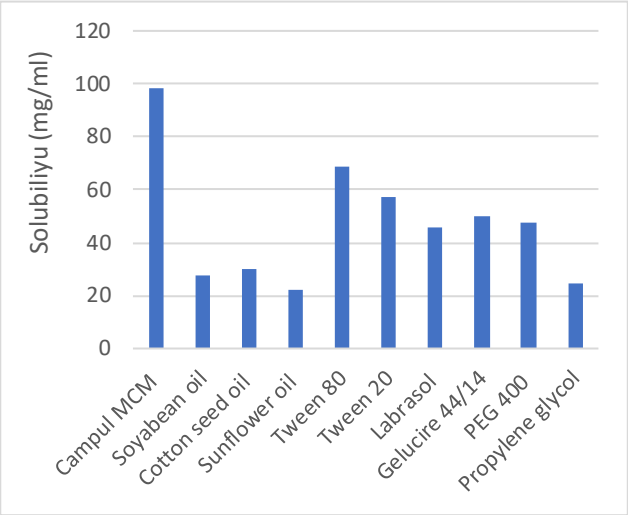

Fig.-1 Cinnarizine solubility in various oils, surfactants and cosurfactants.

Pseudoternary Phase diagram

The construction of pseudoternary phase diagram oil, surfactant, cosurfactant and water. The ratio S/CoS: oil (9:1, 8:2 and 7:3) and S/CoS ratio (2:1, 3:1and 4:1) were selected for the formulation study. In the present study campul MCM was tested for phase behaviour studies with Tween 80 and gelucire 44/14 as the S/CoS mixture. As seen from the ternary plot (Fig.- 2,3 and 4), The ratio S/CoS: oil (9:1) and S/CoS ratio (2:1) give a wider microemulsion region than did all ratio oil and S/CoS ratios. Thus, the choice of oil, surfactant and cosurfactant as well as the ratio of oil to S/CoS have a significant impact on the microemulsion's formation. At the interface surfactant and cosurfactant are preferentially adsorbed, lowering the interfacial energy and acting as a mechanical barrier to coalescence.

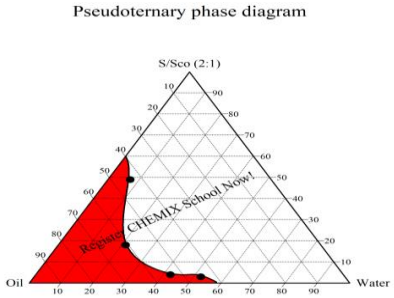

Fig-2

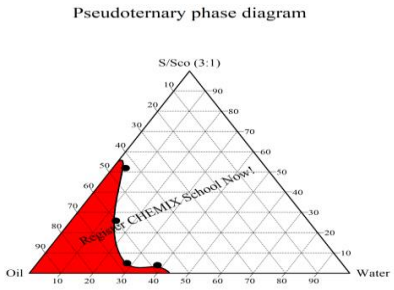

Fig-3

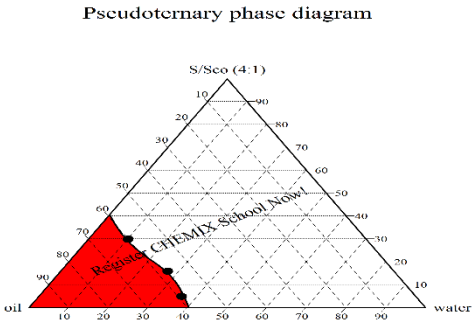

Fig-4

Preparation SMEDDS of Cinnarizine

The number of formulations SMEDDS systems with the ability to dissolve 25 mg of cinnarizine were prepared. During preliminary study, some SMEDDS were eliminated due to detection of oil droplets on the surface of the diluted SMEDDS which transfer to an incomplete emulsification. When mixed with water under mild agitation, SMEDDS that failed to self-emulsify or produced unstable emulsions were rejected. Some SMEDDS formulations were eliminated because they produced milky emulsions when diluted. The transparency of the diluted SMEDDS reflects the proximity of the droplet size to that of the microemulsion range and they were subjected to test for self-emulsification and precipitation assessment (Table-4).

Table-4 Composition of various SMEDDS formulations of Cinnarizine

Formulation Components	Formulation Code								
	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9

Cinnarizine(mg)	25	25	25	25	25	25	25	25	25
Ratio of S: Sco	2:1	2:1	2:1	3:1	3:1	3:1	4:1	4:1	4:1
Ratio of S/SCo: oil	9:1	8:2	7:3	9:1	8:2	7:3	9:1	8:2	7:3
Campul MCM (%)	10.37	21.55	29.10	9.80	19.30	29.75	10.33	19.35	30.23
Tween 80(%)	59.65	52.14	47.22	67.85	60.45	54.23	71.92	64.36	55.62
Gelucire 44/14(%)	29.98	26.31	23.68	22.35	20.25	18.29	17.75	16.29	14.15

Evaluation of Self-emulsification and precipitation study

The self-emulsification efficiency was measured based on the visual appearance, dispersibility and emulsification time. Formulations F-1to F-4 were clear or slightly bluish white and they were graded I and II. Formulations F-5 to F-7 were bright white and they looked like milk. They were graded III and IV. The remaining formulations had large oil droplets on their surface and they were graded V.

Analysis of Emulsion Droplet Size

The parameters used in emulsion droplet size analysis are essential for determine emulsion stability. In SMEDDS the droplet size of the CNZ microemulsion decreased as the oil content was reduced. When Smix: oil ratio was 9:1, the droplet formed was smaller in comparison with ratios 8:2 and 7:3 of S/SCo mix: oil. Generally, 2:1 ratio of surfactant and cosurfactant smaller droplet was formed than 3:1 and 4:1 ratio of S/SCo mix. The smallest droplet size of microemulsion (95.70 nm) was obtained at the 9:1 ratio of S/SCo: oil (Table-5). Formulation F-1 has the highest Tween 80 content (59.46% % wt./wt.)) mixed with oil (10.37% wt./wt.) possess the smallest average particle diameter. This might be explained by a higher proportion of surfactant than cosurfactant. Surfactants are known to stabilize and condense the interfacial film when they are added to microemulsion systems. It is clear that the micro size range depends on the oil concentration and the surfactant/co-surfactant ratio (2:1). Because of their larger surface area these smaller droplets may facilitate greater dissolution of drug and release.

Drug loading efficiency

Drug loading ranged from 76.36 to 92.37 % for all formulations and formulation F-1 to F-3 have maximum drug loading compare to other formulation (Table-5). Then showed a significant variation in drug content across the different formulations.

Table-5 Emulsion Droplet Size and Percent of drug content of SMEDDS cinnarizine

Formulation Code	Size of Emulsion Droplets (nm)	Drug loading efficiency (%)
F-1	95.70	97.87
F-2	98.65	95.29
F-3	101.21	92.46
F-4	108.53	89.32
F-5	117.67	86.28
F-6	132.98	84.98
F-7	151.16	81.71
F-8	165.26	79.53
F-9	188.50	76.36

Dispersibility and optical clearty

As a result, all formulations were visually inspected and their transparency was graded after dilution. Similarly, the percent transmittance of diluted formulations was also noted at 600 nm. After dilution, the formulation with a higher Smix concentration produced transparent emulsions with grade A (Table-6). As a result, when the concentration of surfactant in the formulation increased, the droplet size of the resulting emulsion decreased, resulting in finer emulsions.

Measurement of Zeta potential and polydispersity index

Zeta potential and PDI are important characteristic for drug release following post-systemic absorption. Better stability of the nanosized formulation is indicated by a low zeta potential. As an important fact, low PDI indicates the quality of size distribution, that is uniformity of dispersed system such as microemulsion. The Polydispersibility index value between 0.2 and 0.3(Table-6). These parameters are vital in determining the stability of emulsions. Formulations F-1 to F-3 had zeta potentials below -28.6 mv whereas formulations F-4 and F-9 had higher values. This negative zeta potential suggests that the formulation is more stable because it facilitates drug permeability and formulation stability (Table-6).

Table-6 Dispersibility grade, zeta potential and Polydispersibility index formulations of cinnarizine

Formulation Code	Grade for disperbility	Zeta potential (mv)	Polydispersibility index (PDI)
F-1	A	-23.2	0.219
F-2	B	-25.9	0.226
F-3	B	-28.6	0.241
F-4	C	-30.9	0.259
F-5	C	-33.2	0.272
F-6	D	-35.1	0.289
F-7	D	-38.7	0.295
F-8	E	-41.0	0.312
F-9	E	-43.9	0.333

Test for Robustness to dilution

Formulation of cinnarizine SMEDDS was diluted 100 times using different dissolution media to examine robustness to

dilution namely 0.1 N HCl and phosphate buffer (pH6.8). There are no indications of phase separation or drug precipitation after the diluted microemulsions were stored for 12 hours. (Table-7).

Table-7 Robustness to dilution formulations of cinnarizine

Phase separation	Formulation code								
	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9
N HCl & 6.8 pH	No	No	No	No	No	No	No	No	No
Drug Precipitation									
0.1 N HCl& 6.8 pH	No	No	No	No	No	No	No	No	No

Cooling Temp.(° C)	4	4	4	4	4	4	4	4	4
Heating Temp.(° C)	40	40	40	40	40	40	40	40	40
Time (min.)	30	30	30	30	30	30	30	30	30
No of cycle	6	6	6	6	6	6	6	6	6
Phase separation	No	No	No	No	No	No	No	No	No

In Vitro Dissolution Studies

The effect of pH on drug release was examined by analysing the release profile of CNZ in 0.1N HCl and phosphate buffer (pH 6.8). The droplet size decreased, surface area increased allowing more dissolution and drug release. When S/SCo mix: oil ratio was 2:1, the droplet formed was smaller in comparison with ratios 3:1 and 4:1 of S/SCo mix. Generally, at 2:1 ratio of surfactant and cosurfactant, smaller droplet was formed than 3:1 and 4:1 ratio of S/SCo mix. Thus, the drug release from formulation F-1 to F-3 was found to be highest 95.27% and 89.27% after 6 and 24 hr respective and the results of comparative dissolution study of various formulation (Table-8).

Table-8 Percentage of drug release formulations of cinnarizine

Formulation code	Percentage of drug release
F-1	95.27
F-2	91.61
F-3	89.32
F-4	82.75
F-5	79.36
F-6	74.34
F-7	71.82
F-8	69.64
F-9	65.25

Studies of thermodynamic stability

The self-emulsifying performance in all SMEDDS formulations did not significantly alter during the thermodynamic stability study. During the study period, there was no phase separation in the formulation whether it was diluted or not. It was thus determined that every formulation was thermodynamically stable (Table-9). There was no phase separation or drug precipitation observed in the formulation. Thus, these studies confirmed the stability of the developed formulation and its compatibility (Table-10).

Table-9 Phase separation observation (Cooling and heating)

Condition	Formulation code								
	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9

Table-10 Phase separation observation (following centrifugation)

Condition	Formulation code								
	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9
Revolution per minute	2000-3000	2000-3000	2000-3000	2000-3000	2000-3000	2000-3000	2000-3000	2000-3000	2000-3000
Duration (min)	30	30	30	30	30	30	30	30	30
Phase separation	No	No	No	No	No	No	No	No	No

CONCLUSION

Self-microemulsifying drug delivery systems (SMEDDS) are a flexible and successful method for improving the solubility, dissolution and bioavailability of poorly water-soluble drugs. SMEDDS overcome solubility restrictions and facilitate effective drug absorption by spontaneously forming fine microemulsions upon contact with gastrointestinal fluids. The current study successfully developed SMEDDS of CNZ and evaluated its in vitro performance. Various ratios of campul MCM as oil, Tween 80 as surfactant and gelucire 44/14 as cosurfactant were used to create the formulations following initial screening. There are various formulations F-1 formulation showed promising results in the terms of globule size analysis, self-emulsification time, zeta-potential, drug loading efficiency and in vitro drug release. The F-1 formulation zeta potential was -23.2 mV, indicating strong repulsion and good stability between neighbouring, similarly charged globules in dispersion. Formulations haves' polydispersity indices below 0.3, indicating good uniformity in the distribution of droplet sizes following dilution with water. The formulations, F-1 showed highest drug release. It could be concluded that SMEDDS formed from campul MCM as oil, Tween 80 as surfactant and gelucire 44/14 with surfactant co-surfactant ratio (2:1) and Smix-oil ratio (9:1) is a

promising approach to improve the solubility, dissolution rate and hence bioavailability of CNZ.

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