Original Research Article

Development and investigation of novel solid self-nanoemulsifying system loaded with hydrochlorothiazide for the treatment of hypertension

Akhilesh Dubey, Amitha Shetty[1], G. S. Ravi, Manan Christian Kiritkumar[1], Prabhakara Prabhu[1], Srinivas Hebbar, Sally A. El-Zahaby[2]

Department of Pharmaceutics, NGSM Institute of Pharmaceutical Sciences, Nitte (Deemed to be University), [1]Department of Pharmaceutics, Shree Devi College of Pharmacy, Mangalore, Karnataka, India, [2]Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy and Drug Manufacturing, Pharos University in Alexandria, Alexandria, Egypt

Abstract

Objective: The present study was aimed at formulating and evaluating a novel solid self-nano emulsifying drug delivery system (SNEDDS) to increase the solubility and bioavailability of hydrochlorothiazide (HCZ). Enhancing both solubility and bioavailability of drugs remain the cornerstone for achieving successful outcomes of delivery systems. Furthermore, employing nanotechnology-based formulations such as SNEDDS offers important advantage; the most important is the protection of the drug from enzymatic or chemical degradation.

Materials and Methods: Liquid SNEDDS (L-SNEDDS) was prepared by adding a drug to oil, surfactant, and co-surfactant and heated up to at 60°C under continuous stirring. Solid SNEDDS (S-SNEDDS) was prepared by mixing L-SNEDDS with microcrystalline cellulose in 1:1 proportion.

Results: The scanning electron microscopy showed that S-SNEDDS was spherical with an average particle size of 66.9 nm and 69.2 nm for both L-SNEDDS and S-SNEDDS, respectively. *Ex vivo* skin permeation study indicated that 100% drug was released from both the L-SNEDDS and S-SNEDDS formulation SF3 in 3 h. Analysis of variance test showed significant differences (Moderately significant $P < 0.01$) in the values when compared to a marketed product.

Conclusion: The prepared S-SNEDDS helped in improving the solubility of the poorly soluble HCZ, which is a step forward toward bioavailability enhancement and thus increased therapeutic efficacy of the drug.

Keywords: *Ex vivo*, hydrochlorothiazide, self-nanoemulsifying system, solubility, surfactant

Address for correspondence: Dr. Akhilesh Dubey, Department of Pharmaceutics, NGSM Institute of Pharmaceutical Sciences, Nitte (Deemed to be University), Mangalore - 575 018, Karnataka, India.
E-mail: akhilesh@nitte.edu.in

INTRODUCTION

Delivering drugs via oral route represents the most widely and convenient route being the easiest in administration, the most compliant for the patient, in addition to, the possibility to design many dosage forms. Moreover, it is the most economical, especially that, it is characterized by the least sterility constraints. However, the major challenge with the formulation of oral dosage forms lies with their poor oral bioavailability. Various factors such as poor aqueous solubility, lower drug permeability,

Access this article online	
Quick Response Code:	Website: www.jpionline.org
	DOI: 10.4103/jphi.JPHI_29_18

How to cite this article: Dubey A, Shetty A, Ravi GS, Kiritkumar MC, Prabhu P, Hebbar S, *et al*. Development and investigation of novel solid self-nanoemulsifying system loaded with hydrochlorothiazide for the treatment of hypertension. Int J Pharma Investig 2018;8:83-91.

and presystemic metabolism are responsible for this low oral bioavailability.[1] Knowing that almost 50% of drug candidates suffer from low aqueous solubility that limits their oral bioavailability, and results in high variability and less dose proportionality. Consequently, for such drug candidate absorption rate is governed by dissolution in the gastrointestinal tract (GIT). Therefore, the development of appropriate formulation is required to improve the bioavailability and solubility. One of the most popular and commercially available formulations approaches for solving these problems is self-emulsifying drug delivery systems (SEDDS) which have attracted considerable attention from pharmaceutical scientists who want to increase the oral bioavailability of such poorly water-soluble drugs.[2] This system provides a large interfacial area increasing the activity of pancreatic lipase to hydrolyze triglycerides and thereby promote a faster release of the drug and also minimize the irritation due to the interaction between the drug and gut wall.[3] In addition, lipids can affect the oral bioavailability of drugs. Transforming liquid self-nano emulsifying drug delivery system (L-SNEDDS) into solid SNEDDS (S-SNEDDS) helps to overcome problems associated with L-SNEDDS such as stability, low drug loading, irritation that might affect the mucosa of the GIT, and the interactions that can occur between lipids excipients and capsule shell.[4] The anti-hypertensive drug hydrochlorothiazide (HCZ) has low aqueous solubility and 65%–75% bioavailability and does not undergo any first pass metabolism, hence the reduction in its bioavailability is directly linked to its poor aqueous solubility. Thus by formulating the SEDDS of HCZ, will increase the solubility and oral bioavailability of the drug and decrease the dosing frequency. Therefore, better patient compliance can be achieved.[3,5]

The current study is the first to investigate the relevance of formulation of HCZ as S-SNEDDS to solve its biopharmaceutical problems and ensure better stability avoiding liquid dosage forms poor stability.

MATERIALS AND METHODS

Materials

HCZ was provided by Yarrow Chem Ltd., Mumbai, India. Castor oil, olive oil, sunflower oil, corn oil, and peanut oil were provided by K. S oil Ltd., Baroda, India. Oleic acid was provided by Suvidinath laboratories, Baroda, India. Tween 80, span 80, tween 20, polyethylene glycol, microcrystalline cellulose (MCC) was provided by Merck specialties Pvt. Ltd., Mumbai, India. All other chemicals/reagents used were of analytical grade.

Methods

Compatibility studies

The individual components, anhydrous mixtures, and the formulations were examined by Fourier transform infrared (FTIR). S-SNEDDS was mixed with small quantity of IR grade potassium bromide and scanned in the range of 4000–400 cm^{-1} using an FTIR JASCO instrument (Jasco Corporation, Tokyo, Japan).

Construction of pseudo-ternary phase diagrams

The phase diagram of oil, S_{mix} (surfactant: co-solvent) and water was developed using the water titration method. The results were evaluated based on the diagram which showed the highest area of nanoemulsions region was selected for formulation development. Pseudo-ternary phase diagram represents the nanoemulsion system in two dimensions using three axes. It was constructed to examine the formation of O/W emulsion zone using oil, S_{mix}, and distilled water[6] [Table 1].

Formulation of the liquid self-nano emulsifying system (liquid self-nano emulsifying drug delivery system)

The solubility of HCZ in various oils, surfactant, and co-solvent, was estimated by the solubility determination method. Oleic acid showed the highest solubility, and hence, it was selected as an oil phase. Tween 80 and ethanol were selected as surfactant and co-solvent as they showed the highest solubility for HCZ.

Table 1: Composition of S_{mix} for construction of pseudo ternary phase diagram

The mixture	Ratio	Amount of tween 80 (ml)	Amount of ethanol (ml)
S_{mix} A	1:1	30	30
S_{mix} B	2:1	40	20
S_{mix} C	3:1	45	15
S_{mix} D	1:2	20	40

Table 2a: Various formulations for self-emulsifying drug delivery of HCZ (F1-F6)

Ingredients	F1	F2	F3	F4	F5	F6
S_{mix}	1:1	1:1	1:1	1:1	1:1	1:1
Oil	1:9	2:8	3:7	4:6	5:5	6:4
Oleic acid (%)	10	20	30	40	50	60
Tween 80 (%)	45	40	35	30	25	20
Ethanol (%)	45	40	35	30	25	20
HCZ	25 mg	25 mg	25 mg	25 mg	25 mg	25 mg

HCZ: Hydrochlorothiazide

Table 2b: Various formulations for self-emulsifying drug delivery of HCZ (F7-F12)

Ingredients	F7	F8	F9	F10	F11	F12
S_{mix}	2:1	2:1	2:1	2:1	2:1	2:1
Oil oil	1:9	2:8	3:7	4:6	5:5	6:4
Oleic acid (%)	10	20	30	40	50	60
Tween 80 (%)	60	53	47	40	33	27
Ethanol (%)	30	27	23	20	17	13
HCZ	25 mg	25 mg	25 mg	25 mg	25 mg	25 mg

HCZ: Hydrochlorothiazide

L-SNEDDS was prepared by adding drug to oil, surfactant and co-surfactant and heated up to at 60°C under continuous stirring. The obtained mixture was mixed by a vortex until a clear solution formed[6] [Table 2a and b].

Characterization of self-Nano emulsifying drug delivery system

Drug content

The percent drug content of HCZ in L-SNEDDS was estimated by dissolving the appropriate quantity of individual SNEDDS in methanol. Proper dilution of the samples was made and sonicated using ultrasonicator for 15 min then analyzed using double beam ultraviolet-visible spectrophotometer ([UV]-1700 Shimadzu Corporation, Tokyo, Japan) at 271.6 nm and absorbance was recorded.[7]

Percentage transmittance

The percentage transmittance of the system after 100 times dilution was measured at 650 nm using UV-visible double beam spectrophotometer keeping the water as blank.[8]

Dilution potential/robustness on dilution

The prepared formulation was diluted 100 times with distilled water. The emulsion was observed for any precipitation to confirm the stability of the emulsion.[8]

Emulsification time and dispersibility

For evaluation of self-emulsification properties of formulations, 0.1 ml of each formulation was added to 50 ml distilled water under continuous stirring (500 rpm) at 37°C, and then spreadability, dispersibility tendency, and emulsification progress were observed.[9] Based on visual observation, the following grades shown in Table 3 were assigned.

Centrifugation test

To determine the stability of the emulsion under stress condition, centrifugation test was performed. Diluted formulations were centrifuged (Remi centrifuge) at 25°C at 3500 rpm for 30 min and observed for any phase separation and precipitation of drug.[10]

Table 3: Grades assigned to emulsification time and appearance

Grade	Appearance and emulsification time
A	Easily dispersed nano emulsion with clear or bluish appearance that rapidly formed within 1 min
B	Less clear emulsion with a bluish white appearance that rapidly formed within 1 min
C	Fine milky emulsion was formed within 2 min
D	Dull, grayish white emulsion with slightly oily appearance that slowly formed (longer than 2 min)
E	Poor emulsification with large oil globules present on the surface

Viscosity

The viscosity of the optimized formulation was evaluated by Brookfield viscometer LVDV II (Elscolab Netherlands B. V Tolboomweg, The Netherlands) at 25°C. The experiment was performed in triplicate for each sample and results were presented as an average ± standard deviation (SD).

Emulsification time

The emulsification time is the time for a preconcentrate to form a homogenous mixture upon dilution was monitored visually observing the disappearance of SNEDDS and the final appearance of the nanoemulsion in triplicate. A USP dissolution apparatus filled with 500 ml distilled water was employed to perform this test. The paddle speed was adjusted at 50 rpm and temperature was maintained at 37°C. The SNEDDS (1 ml) was added dropwise to the medium by a dropping pipette and the time required for the disappearance of SNEDDS was checked.[11]

Thermodynamic stability

The stable L-SNEDDS formulations after ternary phase studies were subjected to thermodynamic stability tests to evaluate the effect of temperature variation on phase separation of the SNEDDS formulations. During these studies, the formulations were subjected to heating-cooling cycles (4 and 45°C) and freeze-thaw cycles (−21 and +25°C) with storage at each temperature for 2 days and observed visually for any phase separation. During centrifugation stress studies, SNEDDS formulations were subjected to centrifugation at 4000 rpm for 15 min and formulations were visually observed for any phase separation.[12]

In vitro dissolution/release test

In vitro drug release from the formulations and dissolution of the pure drug was carried out using USP type II dissolution apparatus (50 rpm; 37°C ± 0.5°C) in 900 ml of 0.1 N hydrochloric acid (HCl) buffer and 1% sodium lauryl sulphate (SLS). The selected SNEDDS formulations and pure drug were filled in transparent hard gelatin capsule size "00". At predetermined time intervals, 5 ml were withdrawn and the drug concentration was determined by UV spectrophotometer at 271.6 nm. The withdrawn volume was replaced each time with fresh dissolution medium maintained at 37°C ± 0.5°C. All experiments were carried out in triplicate and the results were presented as mean values ± SD.[13]

Emulsion droplet size measurement, zeta potential and poly dispersibility index

Particle size and poly dispersibility index (PDI) as a measure of the distribution of nanoemulsion were determined using dynamic light scattering technique by aid of Malvern zeta sizer instrument.

Formulation of solid self-Nano emulsifying drug delivery system by adsorption on a solid carrier

S-SNEDDS was prepared by mixing L-SNEDDS with MCC in 1:1 proportion. In brief, L-SNEDDS was added dropwise over MCC contained in a broad porcelain dish. After each addition, the mixture was homogenized using a glass rod to ensure uniform distribution of formulation. Resultant damp mass was passed through sieve no. 120 and dried at ambient temperature and stored until further use.[14,15]

Characterization and evaluation of solid self-Nano emulsifying drug delivery system

Drug content

Same procedure was followed as in SNEDDS.

Reconstituted properties of solid self-Nano emulsifying drug delivery system

Dilution study by visual observation

Effect of dilution on S-SNEDDS was observed visually because dilution may better mimic the condition of the stomach after oral administration. In this method, S-SNEDDS (100 mg) was introduced into 100 ml of double distilled water in a glass beaker that was maintained at 37°C and the contents were gently mixed using a magnetic stirrer. As the time passed, the formation of spontaneous emulsion and progress of emulsion droplets were observed. The emulsification ability of S-SNEDDS was judged qualitatively as "good" when clear nanoemulsion formed and "bad" when there was turbid or milky white emulsion formed after stirring.[16,17]

Angle of repose

The angle of repose of S-SNEDDS was determined by the funnel method. The diameter of the powder cone was measured and angle of repose calculated using the following equation.[18]

$$\tan \theta = h/r$$

Bulk density

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined using the following formula.[18]

$$LBD/TBD = \frac{\text{Weight of powder}}{\text{Volume of packing}}$$

Compressibility index (Carr's)

The compressibility of the granules was determined by Carr's compressibility index.[18]

$$\text{Carr's compressibility index (\%)} = \text{TBD-}\frac{LBD}{TBD} \times 100$$

Hausner's ratio

A similar index-like compressibility index has been defined by Hausner. The Hausner's ratio can be calculated by the following formula.[18]

$$\text{Hausner ratio} = \frac{TBD}{LBD}$$

In vitro drug release

The required quantity of S-SNEDDS (equivalent to 25 mg) was filled into hard gelatin capsules. The capsules were placed into a dissolution medium, and the dissolution test was carried out. *In vitro* drug release study was conducted using USP Type II (paddle) apparatus in the dissolution medium 900 ml HCl containing 1% SLS at 37°C ± 0.5°C. Five milliliter sample was withdrawn, and sampling was continued for 150 min over the entire duration of the study. Aliquots were withdrawn at predetermined time intervals, and an equal volume of fresh dissolution medium maintained at 37°C ± 0.5°C was added. After each withdrawal, the sample was filtered through Whatman filter paper (No. 41) and analyzed spectrophotometrically at 271.6 nm for cumulative percentage drug release. Marketed formulation of the drug was also studied to compare drug release.[19]

Zeta potential and droplet size of reconstituted nanoemulsion from solid self-Nano emulsifying drug delivery system

Same methods were followed as in liquid self-emulsifying system.

Differential scanning calorimetry

Measurements were carried out on pure HCZ and S-SNEDDS using the differential scanning calorimetry (DSC) instrument to check for any phase transition behavior.

X-ray diffraction analysis

The physical state of drug HCZ and its S-SNEDDS were characterized by X-ray diffraction analysis (XRD) measurements using X-ray diffractometer.

Scanning electron microscopy

Scanning electron microscopy (SEM) technique was used to investigate the shape and size of the formed particles.

Ex vivo permeation studies

All experiments and protocols described in this study were approved by the Institutional Animal Ethics

Committee (SDCP/172/2016–2017). Male Wistar rats (250–300 g) were sacrificed by CO_2 inhalation method. The intestine was isolated and cleaned properly. Drug release study was performed on rat ileum in beaker with continuous aeration and equilibrated at 37°C ± 0.5°C. One end of rat ileum was tied, and SNEDDS corresponding to 25 mg was put into it followed by tying up of the other end. The ileum was dipped into the dissolution media 50 ml (buffer pH 7.4 and 1% SLS) in the dissolution vessel, and the dissolution study was performed at 50 rpm and 37°C ± 0.5°C. Samples were withdrawn at predetermined time intervals and analyzed at 271.6 nm using UV spectrophotometer. The percent diffusion was calculated and plotted against time. The above procedure was performed for the pure drug, SNEDDS, S-SNEDDS, and marketed formulation and the results were compared. All the experiments were performed in triplicate.[19]

Kinetics of in vitro drug release

To study the release kinetics, *in vitro* drug release data was applied to kinetic models such as zero-order, first order, Higuchi, and Korsmeyer-Peppas. The release data were also processed for regression analysis using MS-excel statistical function.[20-22]

Stability studies

The developed formulation was subjected to stability studies to evaluate its stability and the integrity of the dosage form. The SNEDDS formulations and S-SNEDDS formulations were put into empty hard gelatin capsules (size 00) and subjected to stability studies at 25°C/60% RH, 30°C/65% RH, and 40°C/75% RH. They were withdrawn for analysis over a period of 3 months. The L-SNEDDS and S-SNEDDS formulations were evaluated for clarity of nanoemulsion, emulsification time, *in vitro* drug release, % drug content, particle size, and *t*-90%, i.e., the time taken for 90% drug release.[23]

Statistical analysis

The data were presented as Mean ± SD One-way analysis of variance (ANOVA) followed by post-Dunnet multiple comparison tests to compare the efficiency of the formulations by using Graph pad prism version 4.03.354 software (Graph Pad Software, Inc., San Diego, CA).

RESULTS

Compatibility study

The IR Spectra of HCZ (pure drug) revealed the following peaks: 3356.5 cm^{-1} (NH stretch), 1042–1170 cm^{-1} (aromatic CH stretch), 1581.34 cm^{-1} (NH bend), 1480.1 cm^{-1} (S = O) stretch for HCZ. The IR spectra of S-SNEDDS formulation SF3 revealed the following peaks: 3358.9 cm^{-1} (NH stretch), 1031–1160.94 cm^{-1} (aromatic CH stretch), 1586.16 cm^{-1} (NH bend) 1482.99 cm^{-1} (S = O) stretch for HCZ.

Formulation of liquid self-Nano emulsifying drug delivery system

Oil, surfactant, and co-solvent were selected based on the solubility of the drug. Oleic acid showed the highest solubility of HCZ (44.60 mg/ml) among the tested oils, so it was used as the oil phase. Tween 80 showed the highest solubility of HCZ (40.12 mg/ml) and highest % transmittance, so it was selected as a surfactant. Ethanol showed the highest drug solubility (98.9 mg/ml), and hence ethanol was used as co-solvent. Pseudo-ternary phase diagram was developed using Pro Sim ternary diagram software using the aqueous titration method [Figure 1].

Characterization and evaluation of liquid self-Nano emulsifying drug delivery system

The percentage drug content of all formulations was found to be in the range of 95.88% ± 0.72–99.68% ± 0.21. F1, F2, F3, F4, F7, F8, and F9 showed good result in % transmittance where the obtained range was found to be 93.9% ± 0.39%–99.2% ± 0.63, whereas, the rest of formulations namely F5, F6, F10, F11, and F12 failed to give good result as their % transmittance was found in the range of 71.2% ± 0.26%–87.3% ± 0.29. All the formulations were subjected to stability on dilution study, and it was found that they were all stable with no evidence of precipitation or separation. The results revealed that the formulations F1, F2, F3, F4, F7, and F8 showed Grade A, whereas F6, F9, and F12 showed Grade B. On the other hand, the formulations F5, F10, and F11 were described by being Grade C. All the formulations were subjected to stability on centrifugation and found to be stable with no evidence of precipitation and phase separation. All the formulations were evaluated for viscosity by Brookfield viscometer at 25°C and were found to have a viscosity in the range of 28–44 cps. The emulsification time for all formulations was found to be from 23 to 41 s and all the formulations passed thermodynamic stability study. Among the 12 set of formulations, it was found that F3 showed the fastest drug release when compared to the rest of formulations. The formulation F3 showed the highest percentage of drug release, where, 100% HCZ were released in 60 min [Figure 2]. Therefore, F3 was selected as the best formulation for further studies and was used for the formulation of S-SNEDDS by adsorption process. The average particle size of formulation F3 was found out to be 66.9 nm and the PDI was found out to be 0.459. The Zeta potential of formulation F3 was found out to be −24.89 mV.

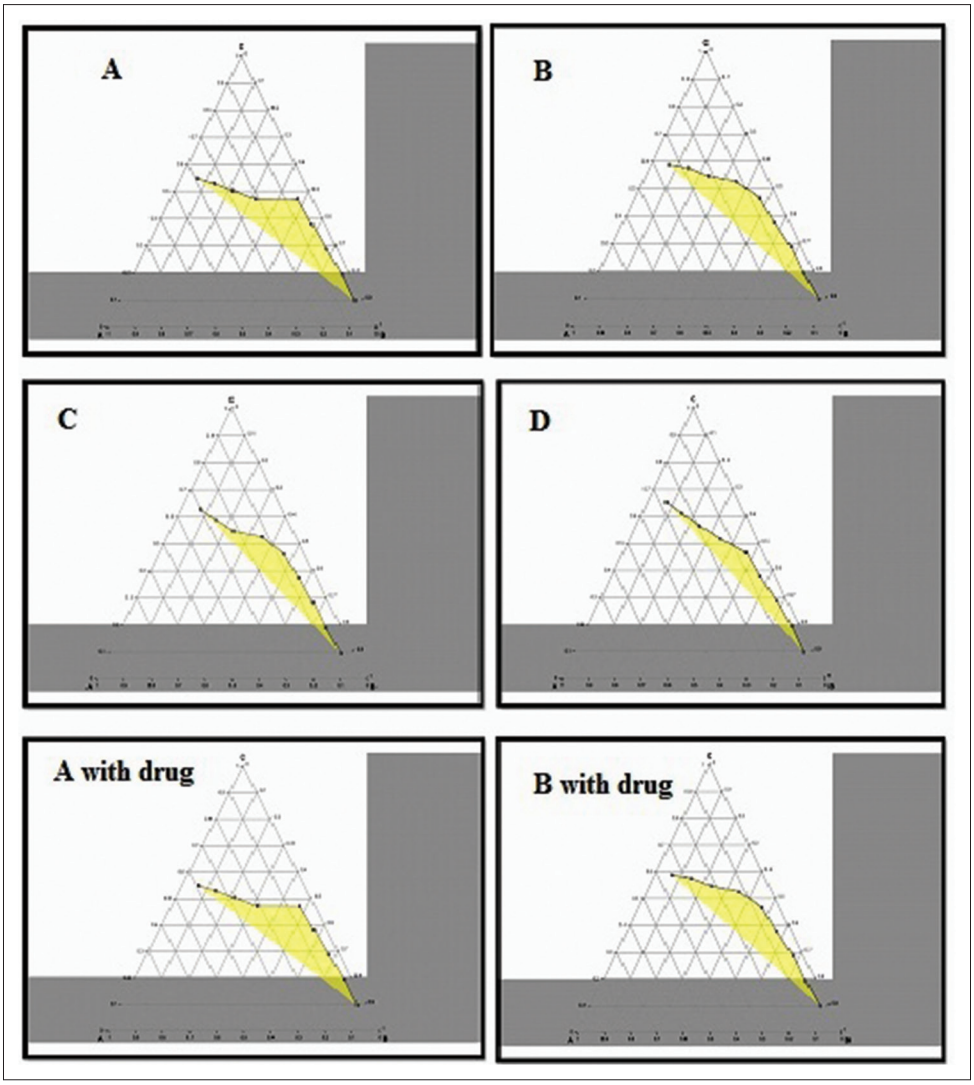

Figure 1: Ternary plots for formulation of system (A-D) system A with drug and system B with drug

Formulation and evaluation of solid self-Nano emulsifying drug delivery system by adsorption on a solid carrier

Formulation F3 was selected for conversion from L-SNEDDS (F3) to S-SNEDDS (SF3). S-SNEDDS was prepared by mixing L-SNEDDS with MCC in 1:1 proportion. Resultant damp mass was passed through sieve no. 120 and dried at ambient temperature and stored until further use.

The percentage drug content of the formulation SF3 was found out to be 99.20%. The formulation SF3 was subjected to dilution study, and it was found to be stable after dilution with no evidence of precipitation or phase separation. The angle of repose of formulation SF3 was found out to be 26.52. The bulk density of formulation SF3 was found out to be 0.53 (LBD) and 0.61 (TBD). The compressibility index of formulation SF3 was found out to be 15.26 which revealed good flow property of the formulation. The Hausner ratio of formulation SF3 was found out to be 1.09. Figure 2 shows the *in vitro* cumulative percent release of HCZ from the 12 prepared L-SNEDDS in 0.1 N HCl and 1% SLS at 37°C ± 0.5°C. *In vitro* drug release behavior of the S-SNEDDS "SF3" in 0.1 N HCl and 1% SLS at 37°C ± 0.5°C was also noted. The Zeta potential of formulation F3 was found out to be-22.92 mV. The average particle size of formulation SF3 was found out to be 69.2 nm, and the PDI was found out to be 0.486. Figure 3a is the DSC spectra of drug HCZ, and the melting endotherm was observed at 264.25 and the thermogram of the formulation SF3, Figure 3b, showed a peak at 107.39°C, which is corresponding to the dehydration of bound water in MCC. Figure 4a corresponding to the XRD of HCZ, the diffraction angles (2 θ) were observed at 10.749, 16.714, 18.279, 20.61, 20.97 and 23.21 and thus indicated the drug in the crystalline form. Whereas in Figure 4b, the peaks

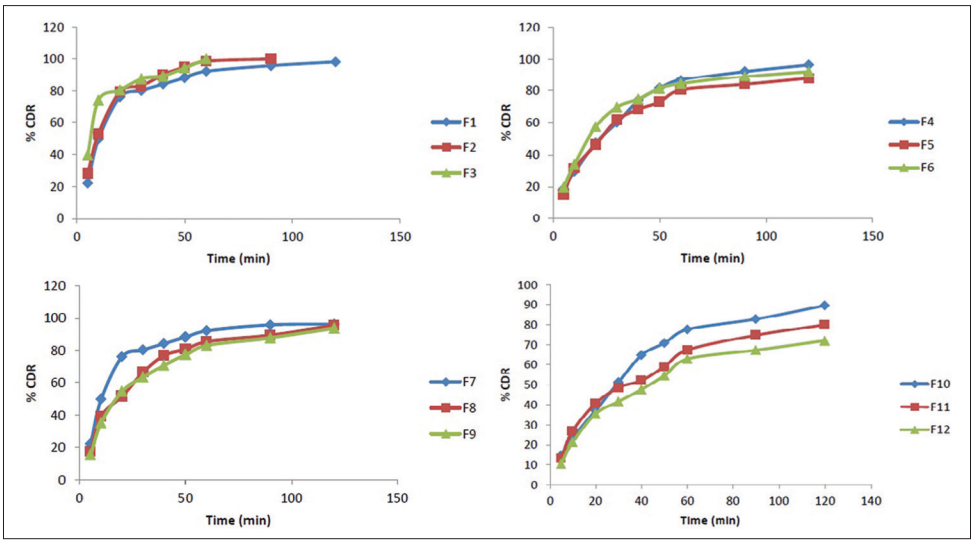

Figure 2: *In vitro* release study of hydrochlorothiazide from Liquid self-nano emulsifying drug delivery system in 0.1 N Hydrochloric acid and 1% sodium lauryl sulphate at 37°C ± 0.5°C

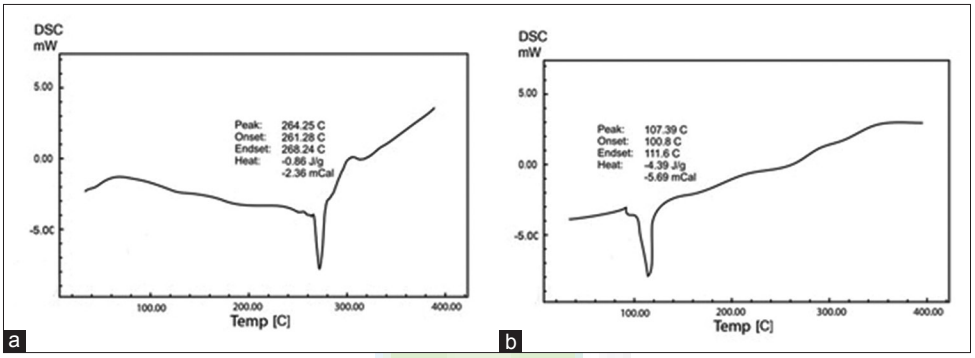

Figure 3: Differential scanning calorimetry of pure drug hydrochlorothiazide (a) and formulation SF3 (b)

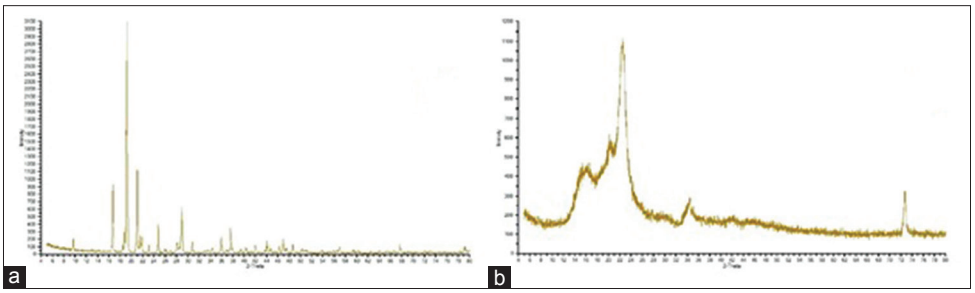

Figure 4: X-ray diffraction of pure drug hydrochlorothiazide (a) and solid self-Nano emulsifying drug delivery system formulation SF3 (b)

observed were corresponding to MCC (carrier used for preparing S-SNEDDS) as the 2 θ values range broadly between 14 and 22 and a peak at 26. SEM was carried out to reveal the morphology of the S-SNEDDS of HCZ. The photomicrograph indicated uniform surfaces of the formed S-SNEDDS [Figure 5].

The *ex vivo* permeation studies revealed 100% drug release for L-SNEDDS formulation F3 and S-SNEDDS formulation SF3 in 180 min (3 h). The pure drug showed 77.44% drug release in 240 min (4 h), and the marketed tablet showed 90.21% drug release in 240 min (4 h) [Figure 6]. After 90 days (3 months), the drug content was found out to be 99%, and the particle size was found out to be 68 nm. The Zeta potential was found out to be-24 mV. The *in vitro* drug release was found out to be 100% at 60 min. The ANOVA test was carried out on the *in vitro* drug release data of prepared formulations at 60 min where all the formulations were compared with the best formulation F3.

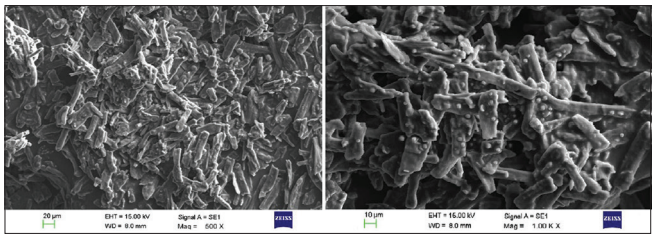

Figure 5: Scanning electron microscopy result of solid self-nano emulsifying drug delivery system of formulation SF3

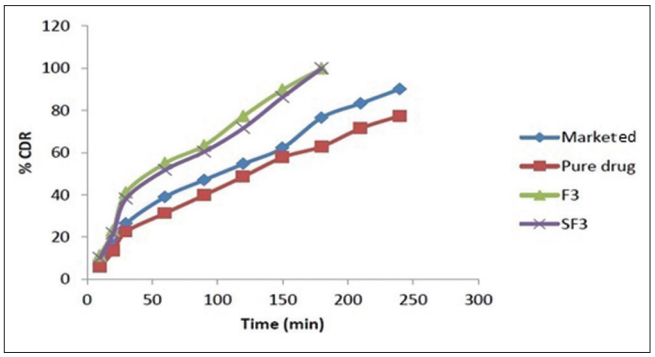

Figure 6: *Ex vivo* permeation study showing the % cumulative drug released from the pure drug, the liquid and solid self-nano emulsifying drug delivery system of hydrochlorothiazide compared to the marketed product

DISCUSSION

HCZ is ingested orally in treating hypertension. However, the oral use of the marketed tablet is followed by various drawbacks including the low solubility, low bioavailability and increased dosing frequency.[24] In the current work, an attempt was made to formulate and evaluate S-SNEDDS using oleic acid, tween 80, and ethanol. The L-SNEDDS was prepared by continuous stirring of the oil phase, surfactant, and co-solvent at 60°C. The FTIR analysis carried out for the pure HCZ , and the formulations showed no change in the signal peaks thus clearly indicating the absence of any interactions between the ingredients. The optimized formulation showed a size of 66.9 nm and a PDI value of 0.459 exhibiting smaller and good uniformity in the size of the particles. The zeta potential was found to be-24.89 mV which revealed that the emulsion was stable. The S-SNEDDS was prepared by mixing L-SNEDDS with MCC in 1:1 proportion. The SEM photographs showed that the SNEDDS of HCZ were spherical in shape. DSC thermograms of pure drug HCZ and formulation SF3 were carried out. Sharp endothermic peak was observed at 264.25°C temperature, which corresponds to the melting temperature of the HCZ. The solid formulation SF3 showed no endothermic peak at melting temperature of drug, and the peak was observed at 107.39°C, suggesting conversion of the crystalline drug to an amorphous state. The XRD pattern for HCZ powder shows the characteristic sharp peaks at a particular diffraction angle. This crystalline pattern was not found in the XRD plot of solid SNEDDS. This further confirmed that the drug presented in an amorphous form. Hence, it was confirmed a complete conversion from crystalline to amorphous form of the drug.[25] The FTIR analysis showed no change in the signal peaks thus clearly indicating the absence of any interactions between the ingredients. The *in vitro* drug release of formulation SF3 showed quick drug release of 79.30% only in 20 min. The formulation SF3 showed 100% percentage drug release in 60 min. The formulation SF3 did not show any significant changes in *in vitro* drug release when compared with the liquid SNEDDS formulation. Hence there was a successful conversion of liquid SNEDDS formulation to S-SNEDDS formulation by adsorption process. The optimized formulation showed a size of 69.2 nm and an L-SNEDDS DI value of 0.486 exhibiting smaller and good uniformity in the size of the particles. The zeta potential was found to be −22.92 mV which revealed that the emulsion was stable.[26] The *ex vivo* permeation studies revealed 100% drug release for L-SNEDDS formulation F3 and S-SNEDDS formulation SF3 in 180 min (3 h). The pure drug showed 77.44% drug release in 240 min (4 h), and the marketed tablet showed 90.21% drug release in 240 min (4 h). Hence from *ex vivo* studies, it was concluded that formulation F3 and SF3 showed faster drug release when compared to pure drug and marketed tablet. Hence, it revealed that the solubility was increased to 30% when compared to marketed tablet. The results of *in vitro* drug release were subjected to kinetic studies for all the formulations, and the results revealed that all the formulations released the drug by zero-order kinetics. Higuchi's model was applied to the *in vitro* release data, linearity was obtained with respect to high "R^2" value, but the "R^2" value was found to be less than the "R^2" value of Korsemeyer-Peppas. The finalized formulation SF3 showed n value of 0.36; hence, Fickian mechanism was involved in its release. The formulation SF3 was subjected to stability studies, and after 90 days the stability study revealed that there were no many significant changes in any characterization of the formulation. Hence, the formulation was considered to be stable. The ANOVA test was carried out on *in vitro* drug release of prepared formulations at 60 min where all the formulations were compared with the best formulation, i.e., F3. The "*P*" values were found to be moderately significant. $P < 0.01$. The ANOVA test was also carried out on *ex vivo* drug release between the prepared formulations and the marketed product considering the % drug release. The "*P*" values were found to be moderately significant for all the formulations when compared to the marketed formulation. $P < 0.01$.

CONCLUSION

HCZ is orally administered for treating hypertension. However, the oral use of the marketed tablet is followed by various drawbacks including the low solubility, low bioavailability, and increased dosing frequency. In the present study, SEDDS of HCZ was formulated to increase the solubility and hence, the oral bioavailability can also be increased. Thus produces a better effect with decrease dosing frequency and hence produces better patient compliance. The developed S-SNEDDS of HCZ in this study has successfully increased the solubility and bioavailability when compared to the marketed drug formulation. The present study showed lot of promise to scale up the method and to investigate further so that the current formulation can become commercially successful.

Acknowledgment

The authors wish to acknowledge the Shree Devi College of Pharmacy, Mangaluru, India for providing necessary facilities and financial support to carry out this project and NGSM Institute of Pharmaceutical Sciences, Nitte University, Mangaluru, India, for logical support and technical guidance.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Krishnaiah YS. Pharmaceutical technologies for enhancing oral bioavailability of poorly soluble drugs. J Bioequiv Availab 2010;2:28-36.
2. Katteboina S, Chandrasekhar P, Balaji S. Approaches for the development of solid self-emulsifying drug delivery systems and dosage forms. Asian J Pharm Sci 2009;4:240-53.
3. Beg S, Swain S, Singh HP, Patra ChN, Rao ME. Development, optimization, and characterization of solid self-nanoemulsifying drug delivery systems of valsartan using porous carriers. AAPS PharmSciTech 2012;13:1416-27.
4. Lipinski CA. Drug-like properties and the causes of poor solubility and poor permeability. J Pharmacol Toxicol Methods 2000;44:235-49.
5. Kale AA, Patravale VB. Design and evaluation of self-emulsifying drug delivery systems (SEDDS) of nimodipine. AAPS PharmSciTech 2008;9:191-6.
6. Patel J, Kevin G, Patel A, Raval M, Sheth N. Design and development of a self-nanoemulsifying drug delivery system for telmisartan for oral drug delivery. Int J Pharm Investig 2011;1:112-8.
7. Kommuru TR, Gurley B, Khan MA, Reddy IK. Self-emulsifying drug delivery systems (SEDDS) of coenzyme Q10: Formulation development and bioavailability assessment. Int J Pharm 2001;212:233-46.
8. Mandawgade SD, Sharma S, Pathak S, Patravale VB. Development of SMEDDS using natural lipophile: Application to beta-artemether delivery. Int J Pharm 2008;362:179-83.
9. Patel HK, Patel PV, Misan CK, Mehta DS, Patel MB. Development and characterization of liquid and solid self-microemulsifying drug delivery system of Tacrolimus. Asian J Pharm 2014;6:204-11.
10. Shen H, Zhong M. Preparation and evaluation of self-microemulsifying drug delivery systems (SMEDDS) containing atorvastatin. J Pharm Pharmacol 2006;58:1183-91.
11. Patel J, Patel A, Raval M, Sheth N. Formulation and development of a self-nanoemulsifying drug delivery system of irbesartan. J Adv Pharm Technol Res 2011;2:9-16.
12. Xi J, Chang Q, Chan CK, Meng ZY, Wang GN, Sun JB, *et al*. Formulation development and bioavailability evaluation of a self-nanoemulsified drug delivery system of oleanolic acid. AAPS PharmSciTech 2009;10:172-82.
13. Jyothi BJ, Sreelakshmi K. Design and evaluation of self-nanoemulsifying drug delivery system of flutamide. J Young Pharm 2011;3:4-8.
14. Shafiq S, Shakeel F, Talegaonkar S, Ahmad FJ, Khar RK, Ali M. Development and bioavailability assessment of ramipril nanoemulsion formulation. Eur J Pharm Biopharm 2007;66:227-43.
15. Trivedi K, Patel PV, Pujara Z. Development and characterization of liquid and solid self-emulsifying drug delivery system of fexofenadine. J Pharm Investig 2013;5:385-94.
16. Salimi A, Sharif Makhmal Zadeh B, Hemati AA, Akbari Birgani S. Design and evaluation of self-emulsifying drug delivery system (SEDDS) of carvedilol to improve the oral absorption. Jundishapur J Nat Pharm Prod 2014;9:e16125.
17. Bhagwat DA, D'Souza JI. Formulation and evaluation of solid self micro emulsifying drug delivery system using aerosil 200 as solid carrier. Int Curr Pharm J 2012;1:414-9.
18. Corveleyn S, Remon JP. Formulation and production of rapidly disintegrating tablets by lyophilisation using hydrochlorothiazide as a model drug. Int J Pharm 1997;152:215-25.
19. Thakkar H, Nangesh J, Parmar M, Patel D. Formulation and characterization of lipid-based drug delivery system of raloxifene-microemulsion and self-microemulsifying drug delivery system. J Pharm Bioallied Sci 2011;3:442-8.
20. Higuchi T. Mechanism of sustained-action medication. theoretical analysis of rate of release of solid drugs dispersed in solid matrices. J Pharm Sci 1963;52:1145-9.
21. Korsmeyer R, Peppas N. Macromolecular and modeling aspects of swelling-controlled systems. Control Rel Deliv Sys 1983;4:77-90.
22. Ritger PL, Peppas NA. A simple equation for description of solute release II. Fickian and anomalous release from swellable devices. J Control Rel 1987;5:37-42.
23. Kumbhar S, Patil A. Formulation and evaluation of self-emulsifying drug delivery system of carbamazepine. Indian J Pharm Edu Res 2013;47:172-7.
24. Yan YD, Kim JA, Kwak MK, Yoo BK, Yong CS, Choi HG, *et al*. Enhanced oral bioavailability of curcumin via a solid lipid-based self-emulsifying drug delivery system using a spray-drying technique. Biol Pharm Bull 2011;34:1179-86.
25. Shah TJ, Amin AF, Parikh JR, Parikh RH. Process optimization and characterization of poloxamer solid dispersions of a poorly water-soluble drug. AAPS PharmSciTech 2007;8:29.
26. Jaiswal P, Aggarwal G, Harikumar SL, Singh K. Development of self-microemulsifying drug delivery system and solid-self-microemulsifying drug delivery system of telmisartan. Int J Pharm Investig 2014;4:195-206.