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Research Article

DESIGN AND EVALUATION OF SELF-NANOEMULSIFYING DRUG DELIVERY SYSTEMS OF MANIDIPINE FOR ENHANCEMENT OF SOLUBILITY

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ABSTRACT

Objective: The present work is aimed at developing liquid self-nanoemulsifying drug delivery system (liquid-SNEDDS) of manidipine.

Methods: The manidipine SNEDDS is formulated with excipients comprising Capmul MCM as oil phase, Transcutol P as surfactant, and Lutrol L 300 as cosurfactant. The prepared fifteen formulations of manidipine SNEDDS were performed for emulsification time, percentage transmittance, particle size, drug release, *in vitro* dissolution and stability studies. Ternary phase diagram plotted using Chemix software.

Results: The optimized manidipine liquid SNEDDS formulation (F14) subjected to drug-excipient compatibility studies by Fourier-transform infrared spectroscopy and characterized for particle size, zeta potential, scanning electron microscopy, and stability studies. The morphology of manidipine SNEDDS indicates spherical shape with uniform particle distribution. The percentage drug release from optimized formulation F14 (98.24±5.14%) was higher than that of pure drug (39.17±2.98%). The stability data indicated no noticeable change in drug content, emulsifying properties, drug release, and appearance.

Conclusion: Hence, a potential SNEDDS formulation of manidipine developed with enhanced solubility, dissolution rate, and bioavailability.

Keywords: Manidipine, Hypertension, Self-nanoemulsifying drug delivery system, Solubility studies, Capmul MCM.

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INTRODUCTION

The Class II to Class IV drugs of biopharmaceutical classification system suffering with poor water solubility lead to lower intestinal absorption, lower bioavailability. Solubilizing poor water-soluble drugs is a major challenge in pharmaceutical research.

Lipid-based drug formulations increase the relative solubility of drugs in GI track by enhancing absorption. Self-nanoemulsifying drug delivery systems (SNEDDS) lipid-based formulations are most promising technology in drug delivery [1-3]. SNEDDS is defined as pre-concentrate containing a mixture of drug, surfactants, oil, and cosurfactant. The smaller size of SNEDDS improves drug dissolution by increasing area for drug release, absorption and by promoting lymphatic transport of the drug. SNEDDS formulation is used for increasing the solubility, oral bioavailability, and permeability of drug. It also protects the drug from hostile environment in GI track and is used for selective GI targeting drug delivery [4-8].

They have particle size ranging from nanometers to few microns. Based on particle size, they are further classified into SMEDDS and SNEDDS. SMEDDS forms microemulsions consisting of oil droplet size ranging between 100 and 200 nm. SNEDDS contains the droplets whose size is less than 100 nm.

Manidipine is used as an antihypertensive. Manidipine binds to voltage-dependent calcium channels on smooth muscle cells and dissociates them, thus blocking the entrance of extracellular calcium into the cell hence preventing this contraction [9,10]. This produces vasodilation which decreases blood pressure.

The objective of present research is to design and characterize the liquid SNEDDS of manidipine. The ability of SNEDDS to improve dissolution rate is evaluated. The formulated SNEDDS was characterized for emulsification time, percentage transmittance, particle size, drug release, and thermodynamic stability.

MATERIALS AND METHODS

Materials

Manidipine is gifted by Aurobindo pharma limited, Hyderabad. Capryol PGMC and Acrysol K-150 Oleic acid, Lauroglycol, and Transcutol HP are procured from Gattefosse, Mumbai. Labrasol, Tween 20, Acconon, Lutrol L 300, Capmul CMC, Labrasol, Acconon and Lutrol L 300 were generous gift samples from BASF, Mumbai.

Preparation of manidipine standard stock solution

10 mg of working standard manidipine were transferred into a 10 ml volumetric flask and were added 1 ml of phosphate buffer pH 1.2 till the mark to obtain a solution of 1000 µg/ml. The solution diluted with phosphate buffer to get a solution concentration of 100 µg/ml. From this solution, a series of aliquots was prepared for further method development.

Solubility studies

The solubility of manidipine in different oils (Acrysol K-150, Oleic acid, Capryol PGMC, Capmul MCM, and Labrafil), surfactants (Kolliphor ELP, Labrasol, Cremophor EL, Lauroglycol, Transcutol HP, and Tween 20), and cosurfactants (propylene glycol, Span 20 PEG 400, Acconon, and Lutrol L300) were examined by adding excess amount of manidipine (approximately 10 mg) with 2 ml each of the above-mentioned components. The drug was transferred to 5-ml glass vial and was mixed with individual components thoroughly for 10 min. The vials placed in shaker bath at 37±1°C for 72 h to attain homogeneity. The samples were further centrifuged 8000 rpm for 20–30 min at 4°C. The supernatant removed and the drug concentration determined by ultraviolet (UV) at 228 nm [11].

Construction of ternary phase diagrams

The phase diagram constructed base on the solubility of drug in various excipients. Various combinations of oil, surfactant, and cosurfactant were considered for construction of the same.

Surfactant and cosurfactant (S_{mix}) belonging to group were mixed in different weight ratio (1:1, 2:1, and 3:1). The S_{mix} ratios are selected with increasing surfactant concentration with respect to increasing cosurfactant concentration and vice versa. Various weight ratios of oil and S_{mix} ranging from 1:9 to 9:1 (1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, and 9:1) were taking glass vials.

Pseudoternary phase diagram plotted by aqueous titration method, each sample of oil and S_{mix} titrated with aqueous phase. The results tabulated based on transparency and ease of flow of emulsion. A pseudo-three-component phase diagram constructed to mark the physical state of the emulsion with oil on the first axis and surfactant on the second axis and cosurfactant on the third axis [12,13].

Measurement of percentage transmittance

The manidipine SNEDDS reconstituted with distilled water. The resulting emulsion observed visually for any turbidity. The percentage transmittance measured using UV spectrophotometer at 228 nm [14].

Emulsification time

With the use of virtual test method, a predetermined volume of mixture (0.2 ml) diluted with 300 ml of water at a temperature of 37°C using a magnetic stirrer. The tendency of emulsion formation observed [15].

Development of manidipine SNEDDS formulations

The manidipine SNEDDS formulations prepared using Capmul MCM were used as oil phase, and Transcutol P and Lutrol L 300 were used as surfactant and cosurfactant (Table 1). Manidipine (10 mg) was added to oil into glass vial and heated to 40°C. The oily mixture mixed thoroughly with surfactant and cosurfactant. The mixture sonicated for 15 min.

Thermodynamic stability studies

The formulations subjected to freeze cycle (−20°C for 2 days followed by 40°C for 2 days). The stable samples centrifuged at 3000 rpm for 5 min and examined for any phase separation. The formulations with no phase separation selected for further investigation [16].

Determination of drug content

Manidipine formulation (0.2ml) equivalent to 10 mg is taken in volumetric flask and made to 100 ml with phosphate buffer pH 1.2. 1 ml of this solution is taken 10 ml flask made up to 10 ml with buffer. The solution is diluted to 10 µg/ml, absorbance measured at λ_{max} 228 nm against blank. The amount of drug present in 0.2 ml of formulation determined by UV spectrophotometric method and drug concentration determined from standard graph.

$$\% \text{ Drug content} = \frac{\text{Actual amount of drug in SNEDDS}}{\text{Theoretical amount of drug in SNEDDS}} \times 100$$

***In vitro* dissolution studies of manidipine SNEDDS formulations**

The dissolution studies were undertaken with paddle method in pH 1.2 phosphate buffer (900 ml) of various concentrations of manidipine at 37°C and speed of 50 rpm. The liquid SNEDDS whose weight equivalent to 10 mg of manidipine was filled into hard gelatin capsules, and samples were withdrawn at different time intervals of 2, 5, 10, 15, 20, 25, 30, 45, and 60 min and the amount of manidipine analyzed at 228 nm by UV [17,18].

Characterization of manidipine SNEDDS formulation

Drug-excipient compatibility studies

The drug-excipient compatibility checked by Fourier-transform infrared spectroscopy (FTIR) method. An FTIR-8400S Spectrophotometer (Shimadzu, Japan) with total reflectance (ATR) accessory used to record the infrared spectra. Analysis of manidipine and physical mixtures of the drug with the excipients carried out with KBr disc. Eight scans recorded at a resolution of 4 cm^{-1} within frequency range of 400–4000 cm^{-1}.

Determination of droplet size

The droplet size of manidipine SNEDDS formulations determined by photon correlation spectroscopy (Malvern Instrument UK) that measures the size range of 10 to 5000 nm. The formulations placed in an electrophoretic cell after dilution [19].

Determination of zeta potential

The zeta potential of the diluted manidipine SNEDDS formulation measured using a zeta meter system. The SNEDDS diluted in ratio 1:2500 (v/v) and mixed constantly. Zeta-potential of the resulting emulsion measured using a Zetasizer.

Determination of shape and surface morphology

Shape and surface morphology of manidipine SNEDDS scanned using scanning electron microscopy (SEM). The SNEDDS converted to emulsion form and placed on metal stubs coated with gold (HITACHI, S-3700N).

Stability studies

The manidipine SNEDDS formulations pilled in gelatine capsules. Stability studies conducted at 25°C/60% relative humidity (RH) and 40°C/75% RH in stability chambers (Thermolab, Mumbai, India). Samples at specified conditions withdrawn for 6 months. Drug content for each sample was analyzed by UV method [20].

RESULTS AND DISCUSSION

Solubility studies

The manidipine drug solubility is <1 mg/mL. The solubility of manidipine tested in oils phases (Acrysol K-150, Oleic acid, Capryol PGMC, Capmul MCM, and Labrafil). The maximum solubility observed

Table 1: Formulation trials of liquid manidipine self-nanoemulsifying drug delivery system

S_{mix} (Surfactant: cosurfactant)	Oil: S_{mix}	Formulation code	Manidipine (mg)	Oil (Capmul MCM) (ml)	S_{mix} (Transcutol P: Lutrol L 300) (ml)	Water
1:1	1:9	F1	10	0.15	1.35	1.1
	2:8	F2	10	0.3	1.2	1.25
	3:7	F3	10	0.45	1.05	1.4
	4:6	F4	10	0.6	0.9	1.55
	5:5	F5	10	0.75	0.75	1.7
2:1	7:3	F6	10	0.15	0.45	3.6
	8:2	F7	10	1.2	0.3	3.82
	9:1	F8	10	1.35	0.15	3.95
	1:9	F9	10	0.15	1.35	2.75
	2:8	F10	10	0.3	1.2	2.89
3:1	5:5	F11	10	0.75	0.75	4.61
	6:4	F12	10	0.9	0.6	4.72
	7:3	F13	10	1.05	0.45	4.86
	8:2	F14	10	1.2	0.3	4.91
	9:1	F15	10	1.35	0.15	5.2

in Capmul MCM 61.84 mg/ml. This was selected as oil phase for manidipine SNEDDS formulations (Table 2 and Fig. 1).

The solubility of the drug checked in various surfactants Kolliphor ELP, Labrasol, Cremophor EL, Lauroglycol, Transcutol HP, and Tween 20 (Table 3 and Fig. 2) and cosurfactants, PEG 400, Acconon, Lutrol L300, and Span 20 (Table 4 and Fig. 3). The maximum solubility found 41.22 mg/ml of Transcutol HP as a surfactant phase and 133.24 mg/ml of Lutrol L300 as a cosurfactant phase. These were chosen as surfactant and cosurfactant for SNEDDS formulation.

Pseudoternary phase diagram

From the solubility studies, Capmul MCM was chosen as oil, Transcutol P as surfactant, and Lutrol L300 as cosurfactant for SNEDDS formulation. A ternary phase diagram plotted indicating that increase in concentration surfactant and cosurfactant with oil increases the self-emulsifying region. Higher efficiency of self-emulsification observed with an increase in surfactant concentration (Figs. 4-6).

Visual observation

The tendency of emulsion formation observed tested by visual observation method. This was performed by keeping the surfactant and cosurfactant ratio (S_{mix}) as 1:1, 2:1, and 3:1 [21]. Ratios 1:9, 2:8, 3:7, 4:6, and 5:5 of S_{mix} 1:1, 7:3, 8:2, 9:1, 1:9, and 2:8 of S_{mix} 2:1, and 5:5, 6:4, 7:3, 8:2, and 9:1 of S_{mix} 3:1 exhibited rapid formation of emulsion with clear appearance within short time. Based on this data, the ratios for the formulation of SNEDDS were selected (Tables 5-7 and Fig. 7).

Table 2: Solubility of manidipine in different oils

S. No.	Oils	Solubility (mg/ml)
1	Labrafil	40.28
2	Capmul MCM	61.84
3	Capryol PGMC	52.26
4	Oleic acid	10.23
5	Acrysol K 150	45.67

Table 3: Solubility of manidipine in different surfactants

S. No.	Surfactants	Solubility (mg/ml)
1	Cremophor EL	85.11
2	Lauroglycol	125.25
3	Kolliphor ELP	91.21
4	Labrasol	109.81
5	Transcutol HP	241.22
6	Tween 20	35.22

Table 4: Solubility of manidipine in different cosurfactants

S. No.	Cosurfactants	Solubility (mg/ml)
1	Propylene glycol	81.24
2	Acconon	75.94
3	Lutrol L300	133.24
4	Propylene glycol 400	90.11
5	Span 20	61.21

Table 5: Visual observation test for S_{mix} (surfactant: cosurfactant) ratio 1:1

Oil: S_{mix}	Time of self-emulsification (min)	Grade
1:9	<2	III
2:8	<2	III
3:7	<2	III
4:6	<2	III
5:5	<2	III
6:4	<1	I
7:3	<1	I
8:2	>2	IV
9:1	>3	V

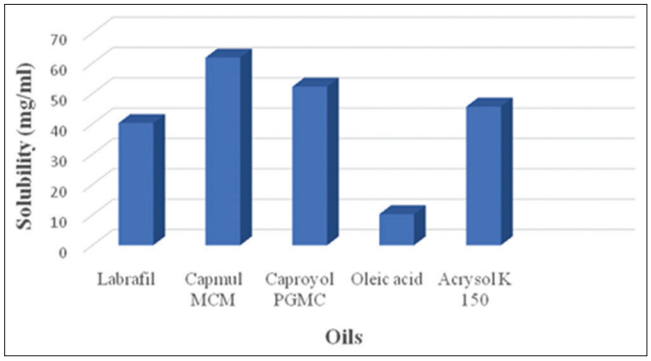

Fig. 1: Solubility studies of manidipine in oils

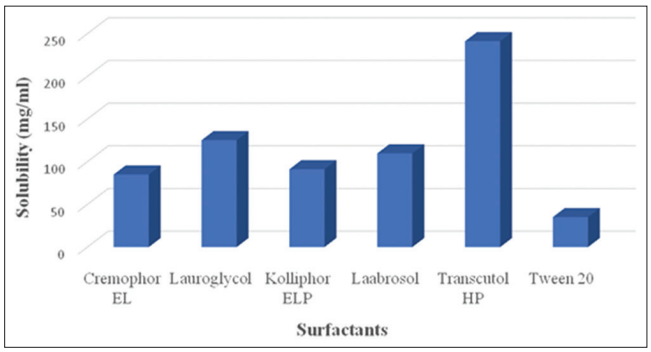

Fig. 2: Solubility studies of manidipine in surfactants

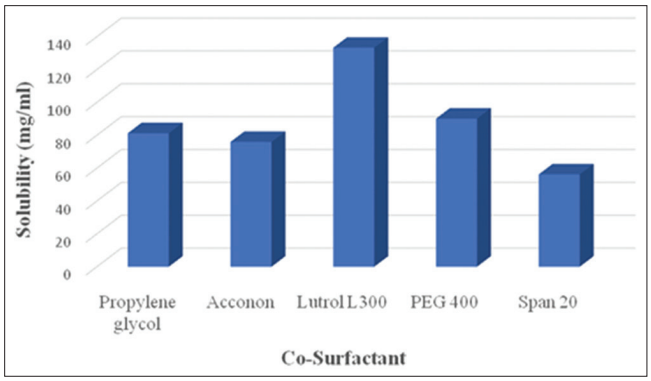

Fig. 3: Solubility studies of manidipine in cosurfactants

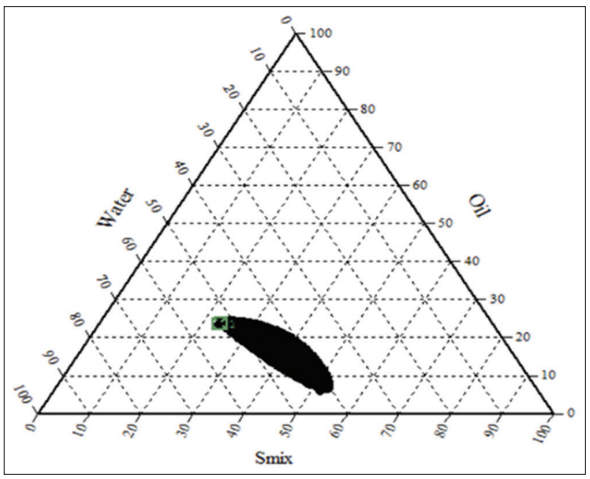

Fig. 4: Ternary phase diagram of Capmul MCM and Transcutol P and Lutrol L300 for 1:1 ratio of S_{mix}

SNEDDS of manidipine formulated using Capmul MCM (oil), Transcutol P (surfactant) and LutrolL300 (cosurfactant). All the fifteen formulations prepared were found to be clear and transparent and their complete composition analyzed (Table 1).

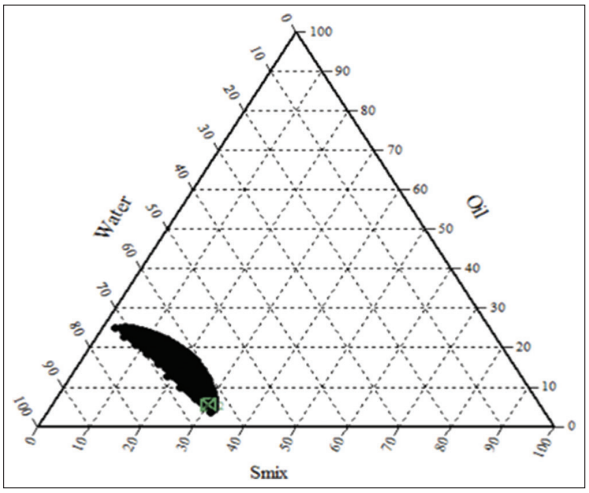

Fig. 5: Ternary phase diagram of Capmul MCM and Transcutol P and Lutrol L300 for 2:1 ratio of S_{mix}

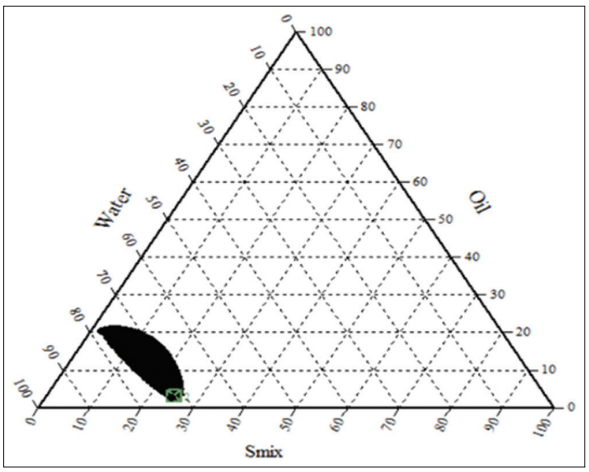

Fig. 6: Ternary phase diagram of Capmul MCM and Transcutol P and Lutrol L300 for 3:1 ratio of S_{mix}

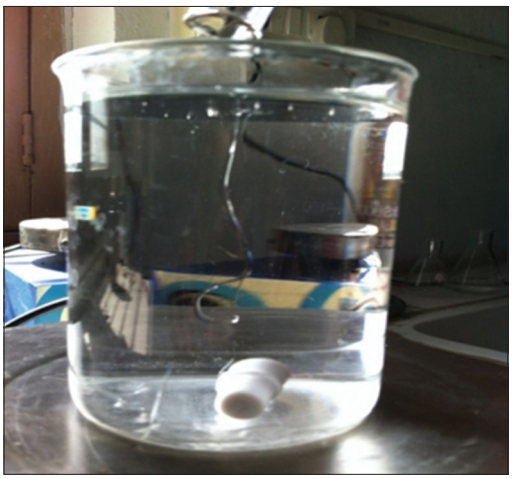

Fig. 7: Preparation of manidipine self-nanoemulsifying drug delivery system

Thermodynamic stability studies of manidipine SNEDDS

The stability studies conducted indicated no significant phase separation or effect of temperature variation on physical appearance of the formulations. No significant change observed visually even after centrifugation freeze-thaw cycles. The thermodynamically stable formulations were selected for further characterization (Table 8).

% transmittance measurement

The transmittance (%T) measures the clarity and transparency of emulsions. Formulation F14 exhibited % transmittance value >99%. Transmittance values were <99% suggesting less clarity of emulsions (Table 9).

Drug content of manidipine SNEDDS

The drug content of the formulated manidipine SNEDDS found to be in the range of 91.19–98.96%. A maximum of 98.96 % was found in the formulation F14 (Table 10).

Table 6: Visual observation test for S_{mix} (surfactant: cosurfactant) ratio 2:1

Oil: S_{mix}	Time of self-emulsification (min)	Grade
1:9	<2	III
2:8	<2	III
3:7	<1	I
4:6	<1	I/II
5:5	<1	I
6:4	>2	IV
7:3	<2	III
8:2	<2	III
9:1	<2	III

Table 7: Visual observation test for S_{mix} (surfactant: cosurfactant) ratio 3:1

Oil: S_{mix}	Time of self-emulsification (min)	Grade
1:9	<1	I
2:8	<1	I
3:7	>2	IV
4:6	<1	I
5:5	<2	III
6:4	<2	III
7:3	<2	III
8:2	<2	III
9:1	<2	III

Table 8: Thermodynamic stability studies of the formulations

Formulation code	Centrifugation	Freeze-thaw method	
		−20°C for 2 days	+40°C for 2 days
F1	NPS	NC	NC
F2	NPS	NC	NC
F3	NPS	NC	NC
F4	NPS	NC	NC
F5	NPS	NC	NC
F6	NPS	NC	NC
F7	NPS	NC	NC
F8	NPS	NC	NC
F9	NPS	NC	NC
F10	NPS	NC	NC
F11	NPS	NC	NC
F12	NPS	NC	NC
F13	NPS	NC	NC
F14	NPS	NC	NC
F15	NPS	NC	NC

#NPS-No phase separation. ##NC-No change

Table 9: %Transmittance of different formulations

Formulation code	Visual observation	Percentage transmittance
F1	Turbid	75.19
F2	Slightly clear	77.07
F3	Slightly clear	78.92
F4	Turbid	76.92
F5	Slightly clear	79.11
F6	Slightly clear	80.21
F7	Transparent	85.04
F8	Transparent	91.77
F9	Slightly clear	84.68
F10	Slightly clear	78.53
F11	Slightly clear	81.24
F12	Transparent	92.37
F13	Transparent	94.37
F14	Transparent	99.21
F15	Transparent	96.25

Table 10: % drug content for various formulations of manidipine self-nanoemulsifying drug delivery system

Formulation code	Percentage drug content
F1	92.37
F2	91.19
F3	92.93
F4	93.99
F5	94.74
F6	93.66
F7	94.67
F8	95.37
F9	94.64
F10	93.44
F11	95.93
F12	94.79
F13	97.99
F14	98.96
F15	94.19

In vitro dissolution studies of manidipine SNEDDS

The drug dissolution studies indicate that the drug release from F14 is higher than that of other fourteen formulations and the pure drug (Figs. 8-10).

Characterization of manidipine SNEDDS

Drug-excipient interactions by FTIR spectroscopy

The FTIR spectra of pure drug manidipine exhibited bands at 3026.41 cm^{-1} due to N-H stretch, at 1640 cm^{-1} for C=O stretching, and at 1226.77 cm^{-1} for aromatic amine group C-N stretching. The spectra also showed bands at 1288.49 cm^{-1} for C-N bending. The FTIR spectrum of SNEDDS containing manidipine exhibited characteristic bands consistent with the molecular structure of manidipine such as bands at 3095.49 cm^{-1} for N-H stretch, at 1678.13 cm^{-1} for C=O stretching, and at 1226.77 cm^{-1} for aromatic amine group C-N stretching. The data indicate no interaction between the drug and excipients used in the formulation (Figs. 11-13).

Particle size analysis of manidipine SNEDDS

The droplet size and polydispersity values of manidipine are analyzed. The particle size of the optimized manidipine SNEDDS formulation (F14) was found to be 22.4 nm and Z-average 23.3 nm. The results indicate that all the particles were in the nanometer range. The polydispersity index of manidipine SNEDDS optimized formulation (F14) was 0.313.

PDI determines the uniformity of particle diameter, and hence, it is useful to know the size distribution of nanoemulsion, which enhances good particle size distribution (Fig. 14).

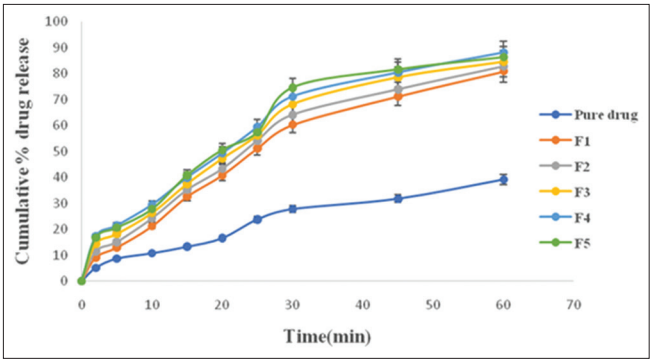

Fig. 8: Dissolution profiles of manidipine pure drug and formulations (F1 to F5)

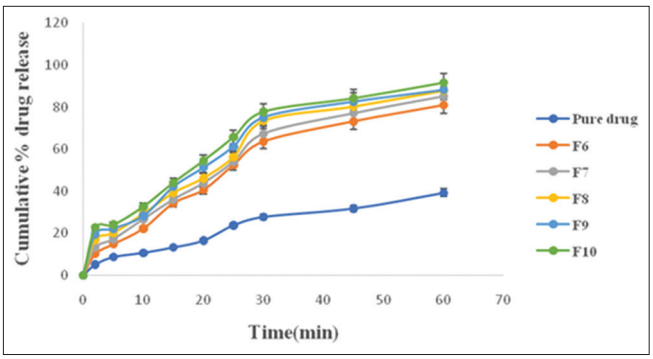

Fig. 9: Dissolution profiles of manidipine pure drug and formulations (F6 to F10)

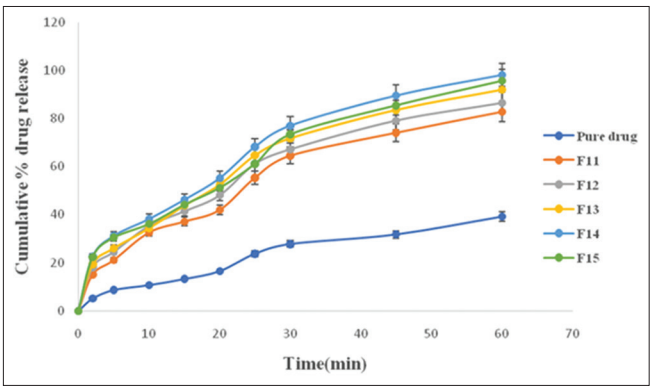

Fig. 10: Dissolution profiles of manidipine pure drug and formulations (F11 to F15)

Zeta potential of manidipine SNEDDS

The zeta potential of the optimized SNEDDS formulation was found to be −5.1 mV which complies with the requirement of the zeta potential for particle stability (Fig. 15).

SEM for manidipine SNEDDS

SEM evaluated the morphology of SNEDDS formulation. The data showed a spherical shape for the optimized SNEDDS (F14) formulation with uniform and relatively narrow particle distribution. Spherical particles could be uptaken easier than disfigured ones. Therefore, it is speculated that the mean particle size that was obtained using the laser diffraction method belongs to the agglomerated SNEDDS particles (Fig. 16).

Stability studies

The stability of optimized manidipine SNEDDS formulation studied for 6 months. The formulation was packed in hard gelatin capsules for the

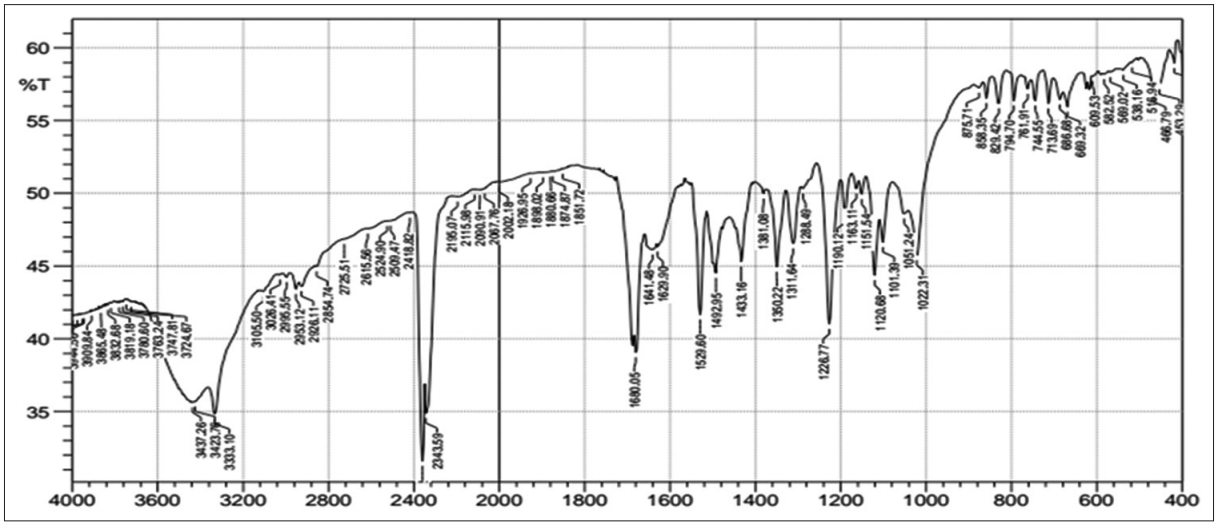

Fig. 11: Fourier-transform infrared spectroscopy spectrum of manidipine pure drug

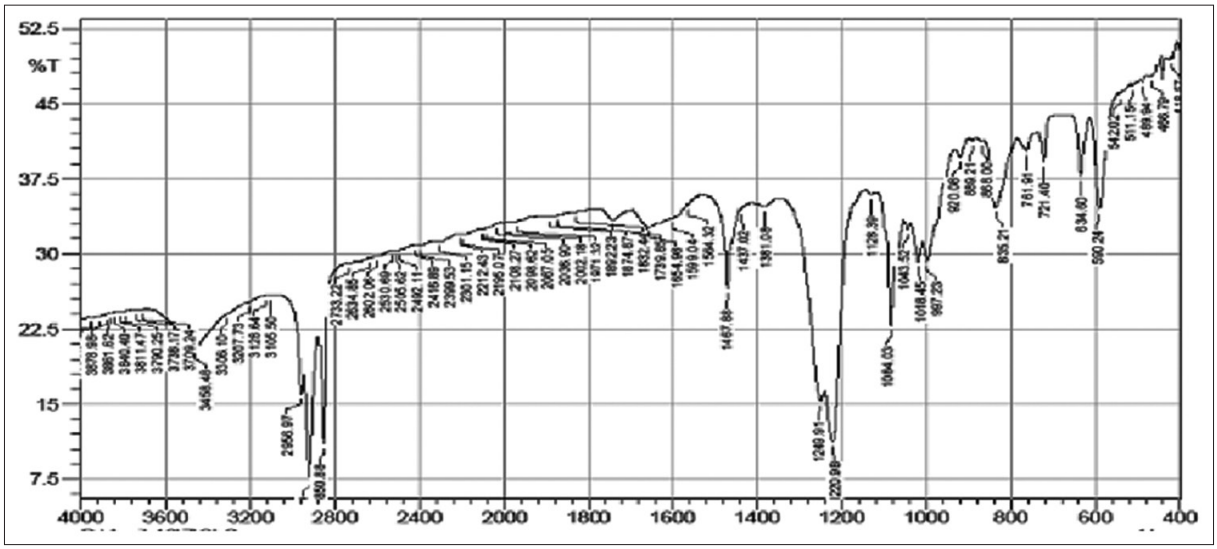

Fig. 12: Fourier-transform infrared spectroscopy spectrum of manidipine physical mixture

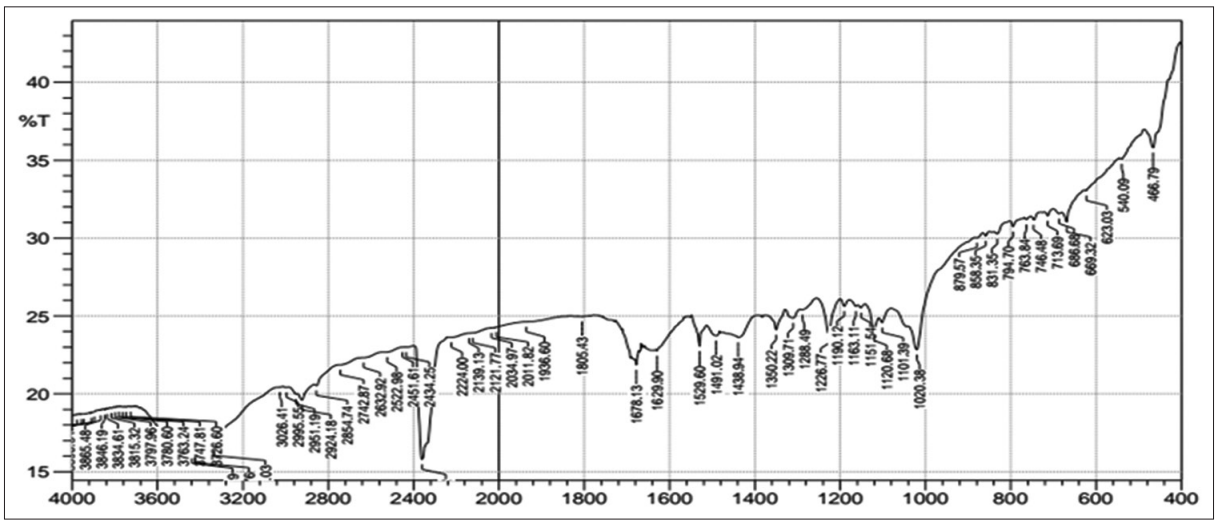

Fig. 13: Fourier-transform infrared spectroscopy spectrum of formulation F14 of manidipine self-nanoemulsifying drug delivery system

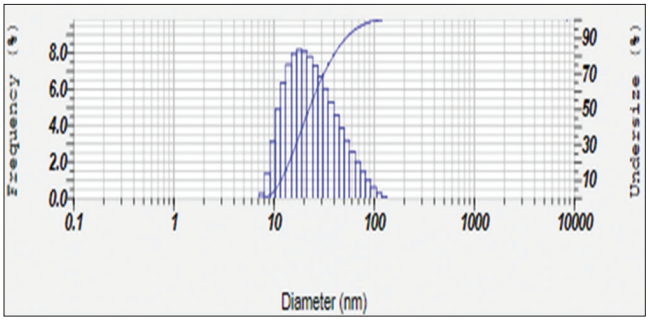

Fig. 14: Particle size analysis of manidipine self-nanoemulsifying drug delivery system formulation F14

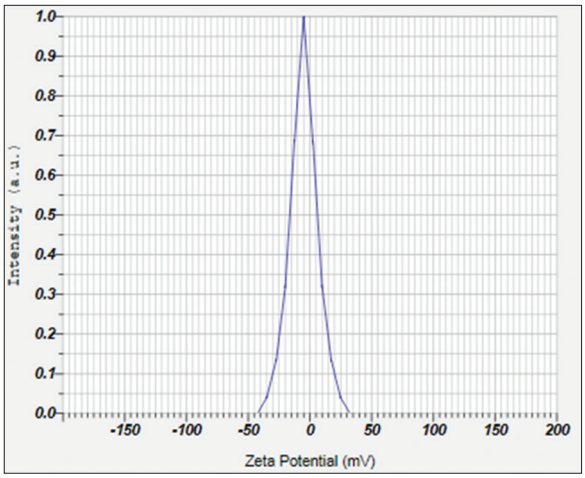

Fig. 15: Zeta potential of the manidipine self-nanoemulsifying drug delivery system optimized formulation F14

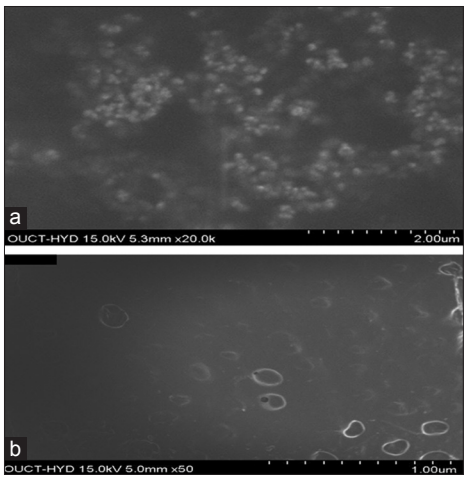

Fig. 16: (a and b) Scanning electron microscopy images of manidipine optimized formulations (F14)

stability studies. The studies indicated no significant variation in drug release and the drug content, physical and emulsifying properties.

CONCLUSION

The present research is aimed at the formulation and characterization of manidipine SNEDDS. The solubility studies indicated maximum solubility of drug in Capmul MCM (oil), Transcutol HP (Surfactant), and Lutrol L300 (cosurfactant). A tertiary phase diagram plotted in accordance with solubility studies indicates that self-emulsifying region was enhanced with increase in the concentration of surfactant and cosurfactant with oil. The visual observation tests indicate that the ratios 1:9, 2:8, 3:7, 4:6, and 5:5 of S_{mix} 1:1, 7:3, 8:2, 9:1, 1:9, and 2:8 of S_{mix} 2:1, and 5:5, 6:4, 7:3, 8:2, and 9:1 of S_{mix} 3:1 showed rapid formation of emulsion within a minute having a clear appearance. Based on the results, fifteen manidipine liquid SNEDDS formulations F1-F15 were prepared and analyzed. The thermodynamic stability studies of all formulations indicate no change in visual description of samples. The % transmittance study indicates that manidipine liquid SNEDDS formulation F14 has a value >99% indicating high clarity of emulsion. The drug content of all formulations ranges from 91.99 to 98.96% with maximum drug content observed in F14 and the maximum drug release found in F14. Hence, F14 is chosen as optimized liquid SNEDDS formulation of manidipine. Drug-excipient studies through FTIR indicated no interaction between manidipine and formulation excipients used. The particle size of F14 is 22.4nm, PI 0.313, and Zeta potential −5.1 mv. The SEM studies of optimized formulation F14 indicated spherical shape with uniform particle distribution. The formulation F14 subjected to stability studies for 6 months indicated no significant change in drug content, drug release, emulsifying properties, and appearance. Hence, a potential liquid SNEDDs formulation of manidipine developed with enhanced solubility, dissolution rate, and bioavailability.

AUTHORS' CONTRIBUTION

Two authors contributed equally.

CONFLICTS OF INTEREST

There are no conflicts of interest by authors.

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