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Research Article

Formulation and Evaluation of Liquid based Supersaturable Self-nanoemulsifying Drug Delivery System of Manidipine

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ABSTRACT

The current research aims to develop a liquid supersaturable self-nanoemulsifying drug delivery system (S-SNEDDS) of manidipine to enhance the solubility and dissolution rate. Cithrol GMS – Cerex ELS250 – Propylene glycol laurate are chosen based on the maximum solubility of manidipine and were used to construct ternary phase diagrams with S_{mix} in 3:1 ratio and 20 mg drug loading was done and evaluated for entrapment efficiency, drug content and *in-vitro* drug release. To choose a precipitation inhibitor, *in-vitro* precipitation studies were carried out, and supersaturable SNEDDS were made. The prepared formulations were evaluated and the final optimized one is characterized for fourier transform infrared (FTIR), scanning electron microscopy (SEM), globule size, zeta potential and stability studies. Out of all formulations F14 exhibited good results with the highest drug content of 98.45 ± 1.39%, entrapment efficiency of 98.91 ± 1.70 %, and drug release of 98.21% in 60 minutes. F14 with PVP K17 (2%) precipitation inhibitor (SF14) exhibited drug content of 99.05% and entrapment efficiency was 99.75% which was almost >1% higher when compared to manidipine SNEDDS (F14). Manidipine S-SNEDDS (SF14) had the maximum drug release (99.85%) in 60 min. SF14 S-SNEDDS had a mean globule size of 162.3 nm and zeta potential (mean) values ranged between -13.1 mV. The FTIR, SEM and stability studies confirmed the complexation of manidipine and amorphous state of the drug and formulation to be stable for 3 months. Thus, this study indicated that the solid SNEDDS could be used as a potential drug carrier for manidipine with improved solubility and dissolution rate.

Introduction

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, and preventing this contraction. This produces vasodilation which decreases blood pressure.[1] It belongs to class II drug in BCS classification with fewer water solubility and reduced bioavailability (50%). Investigation of potential formulation techniques for enhancing manidipine's bioavailability is important.[2]

Various solubility enhancement techniques are employed to enhance the drug solubility and release characteristics, the most acceptable being self-nano emulsifying drug delivery system.

SNEDDS is one method gaining attention due to its ability to increase the solubility of lipophilic agents. It is an isotropic mixture of oil (OL), surfactant (SF) and co-surfactant (CSF) that forms an oil-in-water nanoemulsion (o/w) with slight agitation. The choice of oil is determined by its solubility capacity and the selection of SF and CSF by their emulsification properties.[3]

It is a drug formulation system based on lipids in which drug is entrapped in a lipid stabilized by surfactants that spontaneously form oil in water emulsion on coming in contact with the body fluids. The surfactants decrease the interfacial tension between the fluids and lipid, enabling the drug to get disperse easily and be available for absorption, thus enhancing bioavailability.[4] To overcome the limitations of conventional SNEDSS

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by minimizing drug precipitation in GIT and reducing the amount of surfactant, a new class of supersaturable formulation, namely supersaturable SNEDDS, has been developed as a thermodynamically stable system containing a precipitation inhibitor and less amount of surfactant. Supersaturable-SNEDDS are intended to reduce drug precipitation from solid-SNEDDS in the GI system. Supersaturable SSEDDS are thermodynamically stable compositions with a low surfactant content and a polymeric precipitation inhibitor. Precipitation inhibitors prevent drug precipitation by creating and sustaining a supersaturated condition *in-vivo* after dilution with water.[5]

Manidipine drug has been reported to have limited oral bioavailability and a wide range of first-pass effects, pH-dependent in its solubility and is classified under BCS class II, with low solubility.[6]

Thus, the present work aims to formulate manidipine supersaturable SNEDDS to perk up the solubility and dissolution of manidipine, a poorly soluble drug.

Materials And Methods

Materials used

Manidipine was a kind gift sample from Hetero labs. All other excipients were purchased from Gattefosse, Mumbai.

Solubility of Manidipine in Vehicles

In order to resolve the apparent solubilities of manidipine in various oil, surfactant, and co-surfactant, spectrophotometrically at 242 nm was performed.[7-9]

Construction of Pseudo-ternary Phase Diagrams (TPD)

The chosen vehicles from the solubility studies were blended in altered ratios ranging from 1:9 to 9:1. Each triangle's apex was represented by a TPD containing oil, surfactant, and co-surfactant.[10,11] A pseudo ternary phase diagram is constructed using CHEMIX software.

Effect of Manidipine Loading

A total of 20 compositions of varying ratios of Cithrol GMS – Cerex ELS250 – propylene glycol laurate were taken and in 1-mL composition of each ratio were incorporated with 25, 50, and 75 mg of manidipine (*i.e.,* 18*3=54 formulations). The required amount of manidipine was added to the screw-capped glass vials containing the required amount of surfactant and co-surfactant. Drug was solubilized using a vortex mixer or by heating at 40°C in a water bath wherever necessary. Finally required amount of oil was added to the vials and vortex mixed for 2 minutes for proper mixing. The transmittance of the resulting dispersions up on diluting 25 mg of the formulations with 50 mL distilled water was measured using UV spectrophotometer at 600 nm. The area of nanoemulsification region was identified as described above by constructing pseudo-ternary phase diagrams.[12,13]

Preparation and Evaluation of Manidipine SNEDDS

From a 20 mg loaded manidipine system (which generated more nanoemulsification region based on drug loading), a series of SNEDDS (F1-F15, the composition was presented in Table 1).[14]

Table 1: Composition of manidipine SNEDDS

S. No.	*Formulation code*	*Manidipine drug (mg)*	*Ratios of Oil: Smix*	*Oil (Cithrol GMS)*	*Smix 3:1*	
					Surfactant (Cerex ELS250)	*Co-surfactant (Propylene Glycol laurate)*
1	F1	20	01:01	50	37.5	12.5
2	F2	20	01:02	33	49.5	16.5
3	F3	20	01:03	25	56.25	18.75
4	F4	20	02:01	66	24.75	8.25
5	F5	20	03:02	60	30	10
6	F6	20	05:02	71	21.3	7.1
7	F7	20	02:03	40	45	15
8	F8	20	04:03	57.1	31.95	10.65
9	F9	20	05:03	62.5	28.12	9.3
10	F10	20	07:03	70	22.5	7.5
11	F11	20	08:03	72.7	20.25	6.75
12	F12	20	03:04	42.6	42.6	14.8
13	F13	20	02:05	28.5	53.25	17.75
14	F14	20	02:07	22.2	58.2	19.4
15	F15	20	03:07	30	52.5	17.5

Evaluations

The prepared SNEDDS were characterised for thermodynamic stability studies[15] visual observations,[16] turbidity measurement, robustness to dilution,[17] percentage drug content and entrapment efficiency.[18]

In-vitro Dissolution Study

USP dissolution apparatus II was used to conduct *in-vitro* release tests on produced manidipine SNEDDS. The release tests were 900 mL of freshly prepared pH 1.2 phosphate buffer maintained at 37 ± 0.5°C and the speed of the paddle was set at 100 rpm.[19] The amount of manidipine in each dissolution sample was measured spectrophotometrically at 242 nm, as stated in the literature.[20]

Screening for a Precipitation Inhibitor

In-vitro precipitation experiments were used to estimate the apparent drug concentration-time profile and the duration of the supersaturated state. Polymers such as maltodextrin, soluplus, HPMC E5LV and PVP K17 were employed to stabilize the supersaturated manidipine solution. A 100 mL aliquot of simulated gastric fluid (SGF) was maintained at 37°C with the stirring speed held at 100 rpm. A total of 1-gm of optimized manidipine SNEDDS formulation with various polymers was added to the medium. One milliliter samples of the solution were taken without volume replacement at 5, 15, 30, 45, 60, 90, 120, 180 and 240 minutes, and the aliquots were centrifuged at 3000 rpm for 3 minutes. The supernatant was diluted with methanol, and the concentration of manidipine was assayed by UV analysis at 242 nm.[21]

Evaluation Tests for Supersaturable SNEDDS (S-SNEDDS)

Drug content, entrapment efficiency and *in-vitro* drug release studies were conducted for final S-SNEDDS formulation and compared with pure drug and optimized SNEDDS formulation. The procedure followed was similar to normal SNEDDS.

Characterization of Final Optimized Manidipine S-SNEDDS Formulation

Fourier transformed-infrared spectroscopy,[22] surface morphology (SEM studies)[23] and globule Size and zeta potential[24] were performed.

Accelerated Stability Studies

All formulations filled in hard gelatin capsules were packed in HDPE screw-capped bottles and kept in humidity chambers maintained at 40 ± 2°C/75 ± 5% RH as per ICH guidelines for zone III and stored for 3 months.

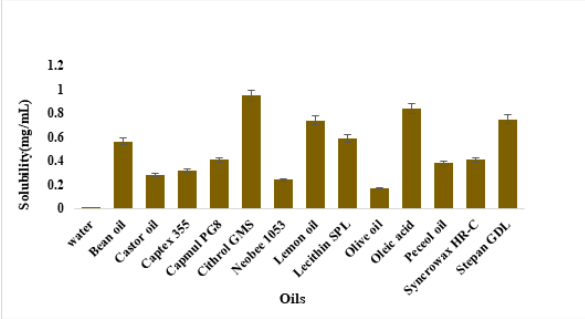
Results And Discussion

Determination of Manidipine Solubility in Various Excipients

Cithrol GMS was selected as oil phase due to its higher solubilization (0.95 ± 0.23 mg/mL) of manidipine compared to other oils (Fig. 1). Surfactant Cerex ELS250 co-surfactant propylene glycol laurate was selected for further studies due to their higher solubilizing capacity towards manidipine (Figs 2 and 3).[25-27]

Construction of Ternary Phase Diagrams

The region of nano emulsification was indicated as shadow area encircled by a solid line and the points indicate the compositions of the system explored. Cithrol GMS – Cerex ELS250 – propylene glycol laurate system with S_{mix} ratio in 3:1 exhibited larger nanoemulsification region as compared to 1:1 and 2:1 S_{mix} ratio (Figs. 4-6).



Above parameters are communicated as Average ± Standard Deviation; (n=3)

Fig. 1: solubility of manidipine in various Oils

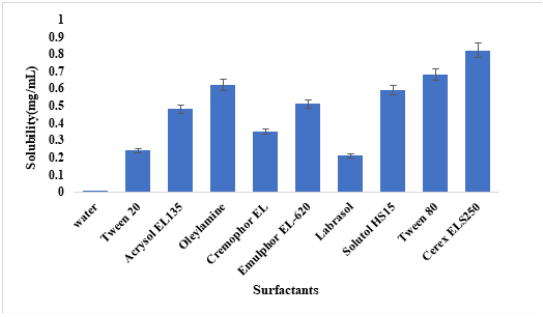


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Fig. 2: Solubility of manidipine in various Surfactants

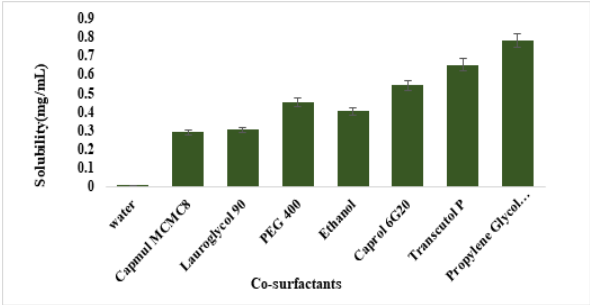

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Fig. 3: Solubility of manidipine in various Co-Surfactants

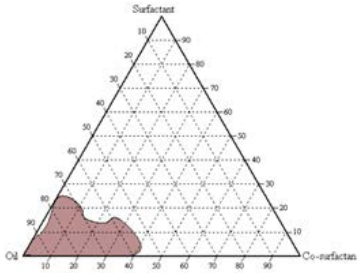


Fig. 4: Ternary phase diagram for Cithrol GMS – Cerex ELS250 – Propylene glycol laurate with S_{mix} in 1:1 ratio.

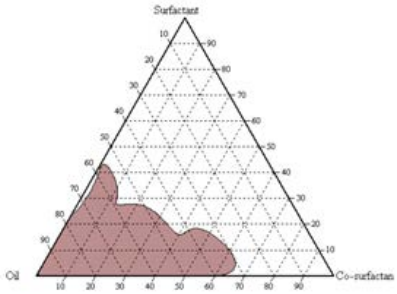


Fig. 5: Ternary phase diagram for Cithrol GMS – Cerex ELS250 – Propylene glycol laurate with S_{mix} in 2:1 ratio.

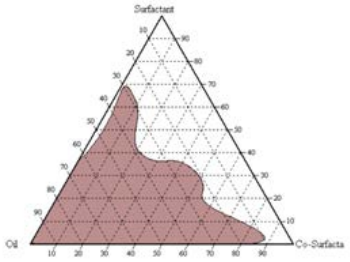


Fig. 6: Ternary phase diagram for Cithrol GMS – Cerex ELS250 – Propylene glycol laurate with S_{mix} in 3:1 ratio.

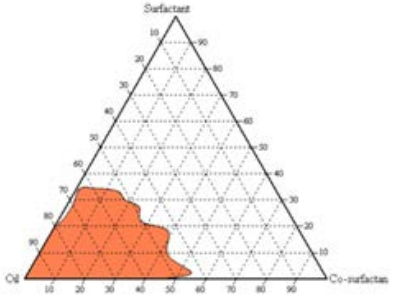


Fig. 7: Ternary phase diagram for 10 mg of manidipine loaded in Cithrol GMS – Cerex ELS250 – Propylene glycol laurate system with S_{mix} in 3:1 ratio.

(Key: the filled region within the ternary phase diagram indicates nanoemulsification area where the transmittance is greater than 90).

The mean globule size was decreased with increase in surfactant concentration. Hence the systems containing Cithrol GMS–Cerex ELS250–propylene glycol laurate with 3:1 S_{mix} ratio were selected for further studies due to their larger nanoemulsifying area, greater capacity for incorporation of oily phase with uniformity of dispersion and high transmittance values (Fig. 6).

Effect of Manidipine Loading

Incorporation of manidipine (10, 20, and 30 mg) led to a considerable decrease in transmittance values (Figs 7-9). The area of nano emulsification was considerably reduced with increase in manidipine loading in to the Cithrol GMS–Cerex ELS250–propylene glycol laurate system with 3:1 S_{mix} ratio hence for the stability reasons of the SNEDDS, system containing 20 mg of manidipine was chosen for formulation of manidipine SNEDDS and further studies.

Preparation and Evaluation of manidipine SNEDDS

From the above results it was found that Cithrol GMS concentration in the range of 22–73% w/w, Cerex ELS250 in the range of 30–60% w/w and propylene glycol laurate in the range of 6-20% w/w in 3:1 of oil: S_{mix} ratio with 25 mg loaded manidipine drug produced the SNEDDS having the transmittance greater than 90, with good stability. A series of SNEDDS were prepared in the above-mentioned ranges of oil- surfactant-co-surfactant ratios and were evaluated for visual observations, turbidity measurements, effect of pH on the mean globule size and zeta potential, robustness to dilution and *in-vitro* dissolution study.

Thermodynamic Stability Studies

Manidipine SNEDDS was tested for centrifugation and the heating-cooling cycle, and passed both tests with no phase separation, creaming, or cracking.

Visual Observations

Visual observations indicated that at higher surfactant levels, the self-emulsification process's spontaneity was increased.[28]

Turbidity Measurement

From these results it can be generalized that the formulations that have low turbidity (<20) gave a transmittance value of more than 90, indicating rapid and spontaneous emulsification within 1-min, hence it gives a good correlation between transmittance and turbidity values.[29]

Robustness to Dilution

Nanoemulsions resulting from the dispersion of manidipine SNEDDS (F1-F15) with distilled water, 0.1N HCl, pH 4.5 acetate buffer and pH 6.8 phosphate buffer were found to be robust to all dilutions and no separation or drug precipitation was observed even after 24 hours of storage.

Percentage Drug Content and Entrapment Efficiency

The drug content of all formulations ranged between 94.78 ± 1.13 to 98.45 ± 1.39% with the maximum value exhibited by F14. The entrapment efficiency of all formulations

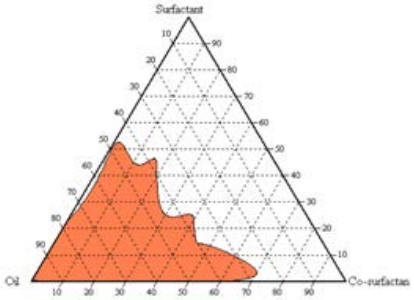


Fig. 8: Ternary phase diagram for 20 mg of manidipine loaded in Cithrol GMS – Cerex ELS250 – Propylene glycol laurate system with S_{mix} in 3:1 ratio.

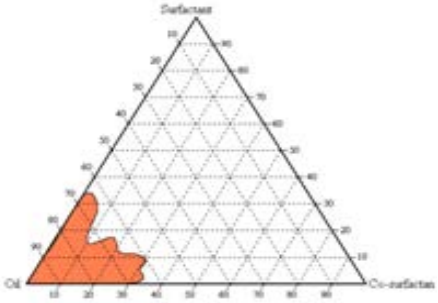


Fig. 9: Ternary phase diagram for 30 mg of manidipine loaded in Cithrol GMS – Cerex ELS250 – Propylene glycol laurate system with S_{mix} in 3:1 ratio.

varies between 94.29 ± 1.39 to 98.91 ± 1.70% with maximum value displayed by F14.

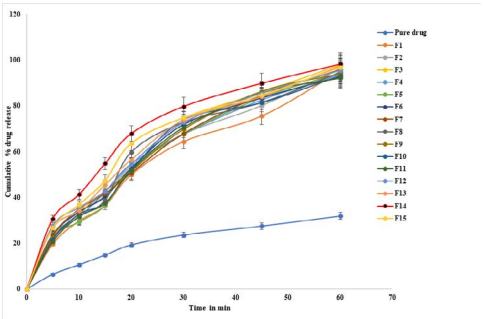
In-vitro Dissolution Tests

Comparative dissolution profiles of manidipine pure drug and manidipine SNEDDS are shown in (Fig 10). Faster release rates were observed for manidipine SNEDDS than the pure drug. Manidipine SNEDDS F1-F15 released more than 60% of drug within 30 minutes, whereas pure drug released 31.84% of drug in 60 minutes. Formulation F14 exhibited highest drug release of 98.21% in 60 minutes. The release of the drug from SNEDDS formulation was increased proportionally with increase in surfactant concentration; hence, F14 exhibited high drug release. Manidipine SNEDDS formulation F14 was selected as the optimized formulation due to the lower turbidity values, faster drug release values among the other SNEDDS.

In-vitro Evaluation of Precipitation

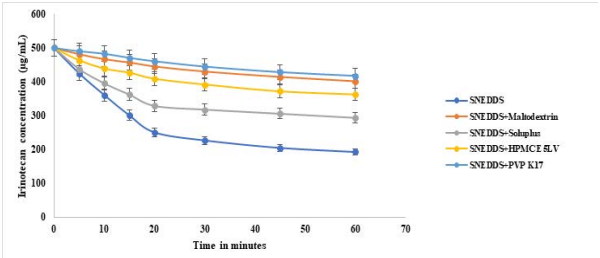
In this study, the degree of supersaturation of the S-SNEDDS was determined using maltodextrin, soluplus, HPMC E5LV and PVP K17 as precipitation inhibitors under non-sink conditions. The total volume of the selected medium was 100 mL, which is equivalent to the total volume of residual stomach fluid based on physiological considerations. The amount of precipitation inhibitor in each formulation was 2% relative to the SNEDDS vehicle. As shown in Fig. 11, the precipitation profiles showed that the S-SNEDDS had better inhibition of manidipine precipitation than the SNEDDS (the same composition but without precipitation inhibitor) during the 60 minutes of the study. Upon mixing with the SGF, the SNEDDS formulation initially appeared as a nanoemulsion with a bluish reflection. After 30 min, solid precipitates of manidipine were observed, which suggested that the medium was in a supersaturated state. For the SNEDDS formulation, at t = 20 minutes, the concentration of manidipine declined to about 250.74 µg/mL, and decreased rapidly to about 192.73 µg/mL after 60 minutes due to the precipitation. In contrast, the S-SNEDDS formulation showed a consistently higher apparent Manidipine concentration-time profile as compared to the SNEDDS formulation.

The manidipine concentration in the S-SNEDDS formulation decreased rapidly when soluplus were applied as the precipitation inhibitors. The concentration declined to < 350 µg/mL within 30 minutes, indicating that soluplus was unable to sustain the apparent Manidipine concentration. Although maltodextrin, HPMC E5LV and PVP K17 could all effectively inhibit Manidipine precipitation, PVP K17 performed better than HPMC E5LV and maltodextrin. Because the highest concentration of manidipine (417.85 µg/mL after 60 min) was observed with PVP K17; for comparison, the concentrations achieved with HPMC E5LV and maltodextrin were 362.74 and 401.61 µg/mL, respectively.



Above parameters are communicated as Average ± Standard Deviation; (n=3)

Fig. 10: Comparative dissolution profile of manidipine pure drug and manidipine SNEDDS formulation (F1-F15).



Above parameters are communicated as Average ± Standard Deviation; (n=3)

Fig. 11: Invitro concentration release profiles of Manidipine from SNEDDS formulation without precipitation inhibitors and S-SNEDDS formulation containing different precipitation inhibitors

Table 2: Accelerated stability studies of manidipine optimised S-SNEDDS formulation (SF14) at 40 ± 2°C/75 ± 5% RH for 3 Months

Retest time for optimized formulation SF14 (S-SNEDDS)	*% Drug content*	*Entrapment efficiency (%)*	*In-vitro drug release (%)*
0 days	99.65 ± 1.75	99.95 ± 0.54	99.85 ± 0.25
30 days	99.11 ± 0.46	99.24 ± 0.48	99.52 ± 0.46
60 days	98.46 ± 0.52	98.76 ± 0.35	99.01 ± 0.57
90 days	98.19 ± 0.59	98.28 ± 1.72	98.79 ± 0.50

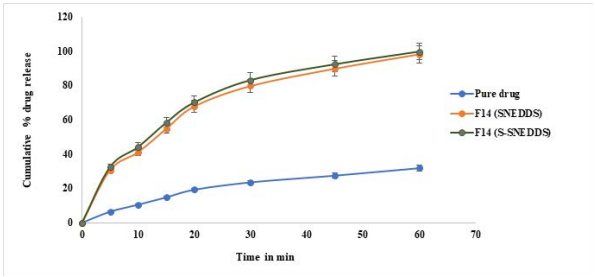


Fig. 12: Comparative dissolution profiles of manidipine pure drug, Manidipine SNEDDS and Manidipine S-SNEDDS.

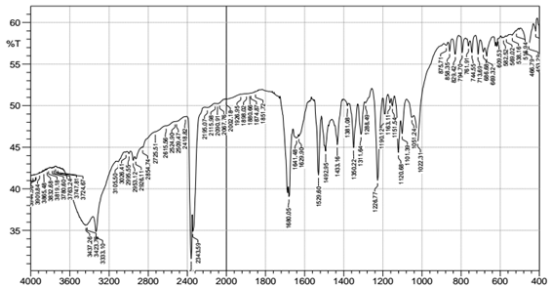


Fig. 13: FTIR spectrum of manidipine pure drug.

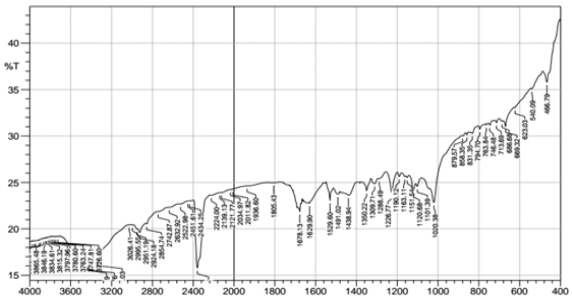


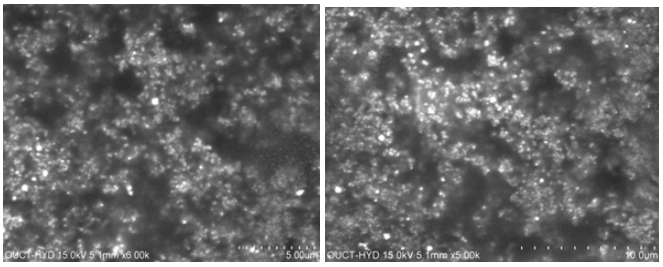
Fig. 14: FTIR spectrum of optimized formulation of Manidipine (SF14).

Drug Content and Entrapment Efficiency

Drug content of manidipine supersaturable S-SNEDDS (SF14) was found to be 99.05% and entrapment efficiency was 99.75%, almost >1% higher, when compared to manidipine SNEDDS F14.

In-vitro Dissolution Studies for S-SNEDDS

In-vitro dissolution studies for S-SNEDDS of formulation SF14 with 2% PVP K17 precipitation inhibitor was studied. Comparative dissolution profiles of manidipine pure drug, Manidipine SNEDDS (F14) and manidipine S-SNEDDS (SF14) is shown in Fig. 12 which indicates the release of drug from manidipine S-SNEDDS (SF14) was highest with 99.85% at the end of 60 minutes



15(A) **15(B)**

Fig 15: SEM images of optimized formulation of Manidipine SNEDDS SF14 (A and B).

Characterization of Manidipine S-SNEDDS (F14) formulation

Fourier-transform Infrared (FTIR) Studies

The FTIR spectra of pure drug (Fig. 13) Manidipine displayed prominent characteristic peaks at 3026.41 cm^{-1} due to N-H stretch, at 1640 cm^{-1} due to C=O stretching, at 1226.77 cm^{-1} due to aromatic amine group C-N stretching. The spectra also showed bands at 1288.49 cm^{-1} due to C-N bending confirming the purity of manidipine.

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} due to N-H stretch, at 1678.13 cm^{-1} due to C=O stretching, at 1226.77 cm^{-1} due to aromatic amine group C-N stretching (Fig. 14).

Scanning Electron Microscopy (SEM) Studies

The scanning electron microscopic pictures of manidipine optimized SNEDDS formulation SF14 are presented in Fig. 15A and 15B. The formulation appeared as spherical and smooth surfaced and analysis of globule size was in accordance with these results with size of all droplets less than 100 nm.

Globule Size and Zeta Potential

The mean globule size of SF14 S-SNEDDS was 162.3 nm and Z average is 113.1, indicating a nanoparticle range that facilitates absorption. The zeta potential (mean) values of SNEDDS formulations were found to be in between -13.1 mV. The zeta potential value > 5 mV provides excellent stability.

Accelerated Stability Studies

No significant difference was observed after storage at accelerated conditions at 40 ± 2° C/75 ± 5% RH for a period of 3 months. (Table 2).

Conclusion

The authors report the successful development of a novel supersaturable SNEDDS formulation of manidipine containing Cithrol GMS – Cerex ELS250 – propylene glycol laurate as oil-surfactant and co-surfactant using 2% PVP K17 polymer as a precipitation inhibitor. When compared, S-SNEDDS (SF14) displayed quicker and highest drug release of (99.85%) in 60 minutes the dissolving profile than the pure drug dispersion and SNEDDS formulation F14. In addition, SF14 S-SNEDDS had a mean globule size of 162.3 nm, indicating nanoparticle range that facilitates absorption and zeta potential (mean) values found to be -13.1 mV providing excellent stability. Further, the FTIR, SEM and stability studies of the final optimized formulation (SF14) showed no interaction of carriers used with the developed self-emulsifying system and found to be stable for 3 months. It can be concluded that the supersaturable SNEDDS formulation effectively improves the solubility and dissolution of poorly water-soluble drug manidipine.

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