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Formulation And In-Vitro Evaluation Of Self Nano Emulsifying Drug Delivery System Of Nifedipine

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Abstract

The aim of the present investigation was to develop a self-nanoemulsifying drug delivery system (SNEDDS) to enhance the solubility and dissolution of poorly water-soluble nifedipine. The solubility of nifedipine in various oils was determined to identify the oil phase of SNEDDS. Various surfactants and co-surfactants were screened for their ability to emulsify the selected oil. A ternary phase diagrams were constructed to identify the efficient self-emulsifying region. The SNEDDS formulations were prepared and evaluated for various tests and final optimised formulation was chosen and characterised for FTIR, DSC, SEM and stability studies. The optimized SNEDDS formulation (F11) contained drug, sesame oil (20%), Labrasol (60) and Triton SP-135 (20%). The optimized formulation of drug-loaded SNEDDS exhibited 98.74% entrapment efficiency, 99.88% drug content and 99.86% *in vitro* drug release in 60 min as compared with the plain drug, which had a limited dissolution rate (31%). The degradation of nifedipine from optimized nifedipine SNEDDS formulation was significantly less when compared to the pure drug degradation. These results suggest the potential use of SNEDDS to improve dissolution and stability of poorly water-soluble nifedipine.

Keywords: Nifedipine**,** Calcium channel blocker, Self-nanoemulsifying drug delivery systems (SNEDDS), pseudoternary phase diagram, Solubility.

Introduction

The oral route is the easiest and most convenient way of noninvasive administration. However, oral drug delivery may hamper drug molecules that exhibit a poor aqueous solubility. Approximately 40% of the new chemical entities exhibit poor aqueous solubility and present a major challenge to the modern drug delivery system, which leads to poor oral bioavailability, high intra- and inter-subject variability and lack of dose proportionality. These drugs are classified as class II drugs by the Biopharmaceutical Classification System(BCS), drugs with poor aqueous solubility and high permeability.(Stegemanna et al., 2007) Various approaches like solid dispersion and complexation with cyclodextrins have been already utilized to resolve the poor aqueous solubility (Chayla et al.,2008) Indeed, in some selected cases, these approaches have been successful, but they offer many other disadvantages like, in solid dispersion, the amount of carriers used is often large and, thus, if the dose of the active ingredient is high, the tablets or capsules formed will be large in volume and difficult to swallow. Moreover, because the carriers used

are usually expensive and the freeze or spray-drying method requires particular facilities and processes, this leads to a high production cost. Although the traditional solvent method can be adopted instead, it is difficult to deal with co-precipitates with a high viscosity. Complexation with cyclodextrin techniques is not applicable for drug substances that are not soluble in both aqueous and organic solvents. Realization that the oral bioavailability of poor water-soluble drugs may be enhanced when co-administered with meal rich in fat has led to increasing the recent interest in the formulation of poorly water-soluble drugs in lipids. Lipid suspension, solutions and emulsions have all been used to enhance the oral bioavailability but, more recently, there has been increasing focus on the utility of self-nanoemulsifying drug delivery systems (SNEDDS). Being hydrophobic, i.e., more lipophilic, a lipid-based drug delivery system would ideally work for a poorly water-soluble drug. (Haus, 2007)

Nifedipine (NF) is a calcium channel blocker which belongs to the dihydropyridine derivatives. It exhibits poor dissolution characteristics due to its poor wettability and dispersibility in body fluids (Acarturk et al,1992). Therefore, a number of attempts, such as decreasing particle size, the use of wetting agents, co-precipitation, preparation of solid dispersions, and self-emulsifying drug delivery systems, have been made to modify the dissolution characteristics and thereby improve the absorption rate. In the present study, the aim was to develop a self-nano emulsifying drug delivery system of a poorly water-soluble nifedipine drug to enhance its solubility thereby dissolution.

Material and Methods

Materials

Nifedipine drug was purchased from Hetero drugs Ltd, Hyderabad. Sesame oil, olive oil, sunflower oil, soybean oil, palm kernel oil, palm oil, corn oil, peanut oil, peceol oil, acrysol EL135, acconon E, acconon Sorb20, cremophor CO 60, tween 20, tween 80, caprol PGE 860, lauroglycol 90, cremophor RH 40, labrasol, labrafac, caproic acid, cremophor EL, caproic acid, transcutol p, triton SP-135, propylene glycol, Capmul MCMC8, PEG 400 and PEG 600 were purchased from Gattefosse, Mumbai. All the reagents used were of analytical grade.

Solubility of Nifedipine in Vehicles

Naturally occurring different vegetable oils, various surfactants and co-surfactants were studied for nifedipine solubility in order to identify the components for construction of ternary phase diagrams. An excess amount of nifedipine was placed in screw-capped glass vials containing 1 g of vehicle (i.e., oil or surfactant or co-surfactant) (Zhang P et al 2008).

Construction of Pseudo-Ternary Phase Diagrams

From the solubility study oil, surfactant and co-surfactant were chosen based on the maximum solubility of the drug in it, the chosen vehicles were mixed in various ratios ranging from 1:9 to 9:1 (oil: Smix). Smix is the mixture of surfactant and co-surfactant prepared in defined ratios of 1:1, 2:1, and 3:1. (Kim. J.Y et al, 2000). The transmittance value more than 90 indicated nano size droplets formation hence these ratios were noted and used for plotting pseudo-ternary phase diagram (Czajkowska-Kośnik, A. et al, 2015). Pseudo ternary phase diagram is constructed using CHEMIX software

Effect of nifedipine loading

The drug loading has considerable influence on the globule size and phase behaviour of the spontaneously emulsifying systems. In the view of this, effect of nifedipine loading on the transmittance, phase behaviour and area of nanoemulsion formation was studied on Sesame oil - Labrasol -Triton SP-135compositions with Smix in 3:1 ratio, which gave more area of nanoemulsification region among the other ratios.

Seventeen compositions of varying ratios of Sesame oil - Labrasol -Triton SP-135 were taken and in 1ml composition of each ratio were incorporated with 30 mg, 60 mg and 90 mg of nifedipine (i.e., 17*3=51 formulations). (Shiva Kumar Mantriet al, 2012).

Preparation of Nifedipine SNEDDS

A series of SNEDDS (F1- F15, the composition was shown in (Table **1**) which showed transmittance values more than 90) were selected from 30 mg loaded nifedipine system and prepared as described above (Czajkowska-Kośnik, A. et al, 2015). About 1ml of the formulation (equivalent to 30 mg of the Nifedipine) was filled in size '00' hard gelatin capsules, sealed and stored at ambient temperature (25° C) until used. These SNEDDS were evaluated for visual observations, turbidity, effect of pH of the dispersion media on globule size and zeta potential, robustness to dilution and invitro dissolution study and were optimized (Bandivadekar MM et al, 2011).

Table 1. Composition of Nifedipine SNEDDS.

S. No	Formulation code	Nifedipine drug (mg)	Ratios of Oil: Smix	Oil (Sesame oil)	Smix 3:1	
					Surfactant (Labrasol)	Co-surfactant (Triton SP-135)
1	F1	30	01:01	50	37.5	12.5
2	F2	30	01:02	33	49.5	16.5
3	F3	30	01:03	25	56.25	18.75
4	F4	30	02:03	40	45	15
5	F5	30	05:02	71	21.3	7.1
6	F6	30	03:02	60	30	10
7	F7	30	08:03	72.7	20.25	6.75
8	F8	30	07:03	70	22.5	7.5
9	F9	30	05:03	62.5	28.12	9.3
10	F10	30	04:03	57.1	31.95	10.65
11	F11	30	01:04	20	60	20
12	F12	30	02:05	28.5	53.25	17.75
13	F13	30	02:07	22.2	58.2	19.4
14	F14	30	03:04	42.6	42.6	14.8
15	F15	30	03:07	30	52.5	17.5

Evaluations of nifedipine SNEDDS

Visual Observations Turbidity Measurement, Robustness to Dilution, Percentage drug content Entrapment efficiency (Khoo SMet al, 1998), (Nasr A et.al, 2016),

In Vitro Dissolution Study

In vitro dissolution studies were performed on developed nifedipine SNEDDS, Nifedipine pure drug using USP dissolution Apparatus II (Lab india DS 8000, Mumbai, India). Hard gelatin capsules, size "1" filled with nifedipine SNEDDS formulation were introduced into 900 mL of freshly prepared pH 6.8 phosphate buffer maintained at 37 ± 0.5° C and the speed of the paddle was set at 50 rpm. Capsules were held to the bottom of the vessel using copper sinkers. At pre-determined time intervals, 5 mL of samples were withdrawn by means of a syringe and immediately replaced with 5 mL of fresh medium maintained at 37 ± 0.5° C (Nilesh Bagul et al., 2012) (Xiangjun Shi et al, 2019). The nifedipine content in each dissolution sample was quantified spectrophotometrically at the wavelength of 230 nm as reported in literature and compared with in-vitro dissolution profiles of nifedipine pure drug (Shakeel, F et al, 2016). All measurements were done in triplicate.

Characterization of optimised nifedipine SNEDDS formulation

Fourier Transformed-Infrared Spectroscopy (Ravula, A.R. et al, 2014), Globule Size and Zeta potential, Scanning electron microscopy (Seo, Y.G. et al, 2015).

Forced Degradation and Accelerated Stability Studies

Nifedipine is very susceptible to decomposition when it is exposed to oxygen, light, temperature, humidity, carbon dioxide and acidic pharmaceutical excipients. The percentage degradation of nifedipine was calculated (ICH Harmonized Tripartite guideline on “Stability Testing of NewDrug Substances and Products Q1A (R2)”, 6 February 2003).

Accelerated Stability Studies

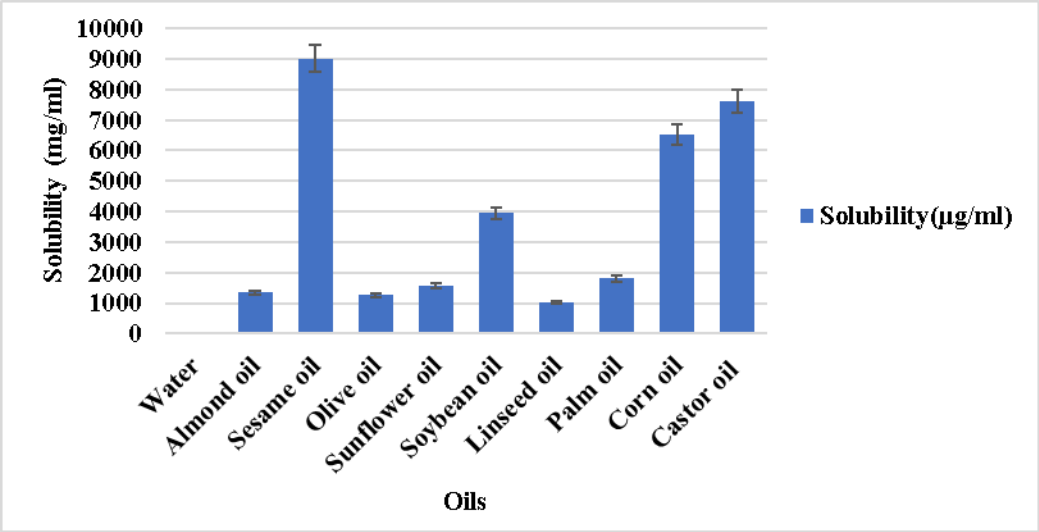
Optimised formulation was filled in hard gelatin capsules were packed in HDPE screw capped bottles and kept in humidity chambers maintained at 40 ± 2°C/ 75 ± 5% RH as per ICH guidelines for Zone III and stored for 6 months. Samples were evaluated for entrapment efficiency, drug content and drug release (ICH Harmonized Tripartite guideline on “Stability Testing of NewDrug Substances and Products Q1A (R2)”, 6 February 2003).

Results and Discussion

Determination of nifedipine solubility in various excipients

Sesame oil was selected as oil phase due to its higher solubilization (9011.115±1.27 mg/g) of Nifedipine compared to other oils (Figure 1).

Figure 1. Solubility of Nifedipine in various Oils.



Surfactant Labrasol and co-surfactant Triton SP-135were selected for further studies due to their higher solubilizing capacity towards Nifedipine (Reiss, Het al, 1975), (Craig, D.Q. Metal, 1995). (Constantinides, P. Pet al, 1997). (Figure 2 and 3).

Figure 2. Solubility of Nifedipine in various Surfactants.

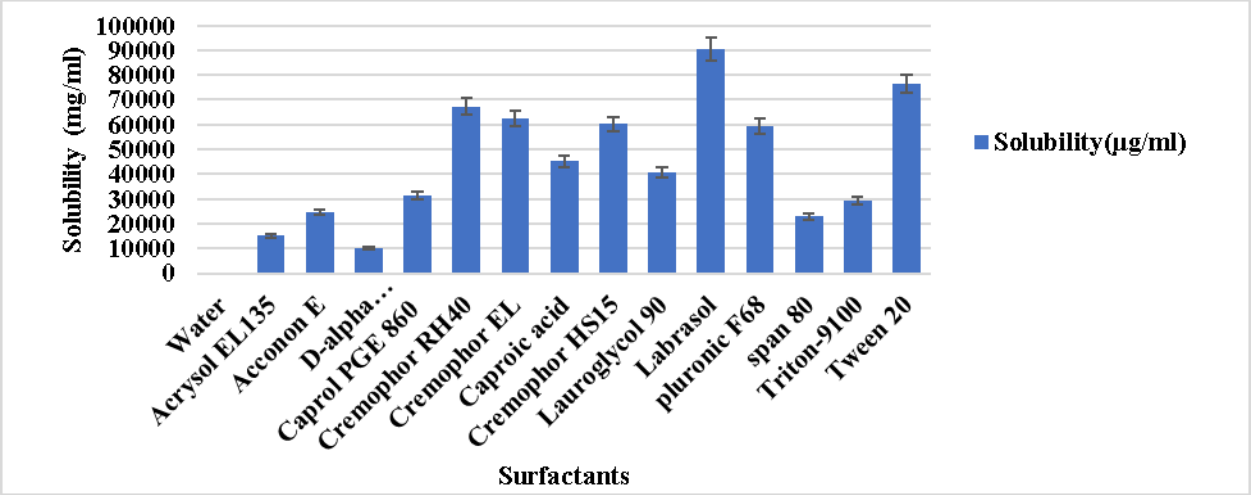
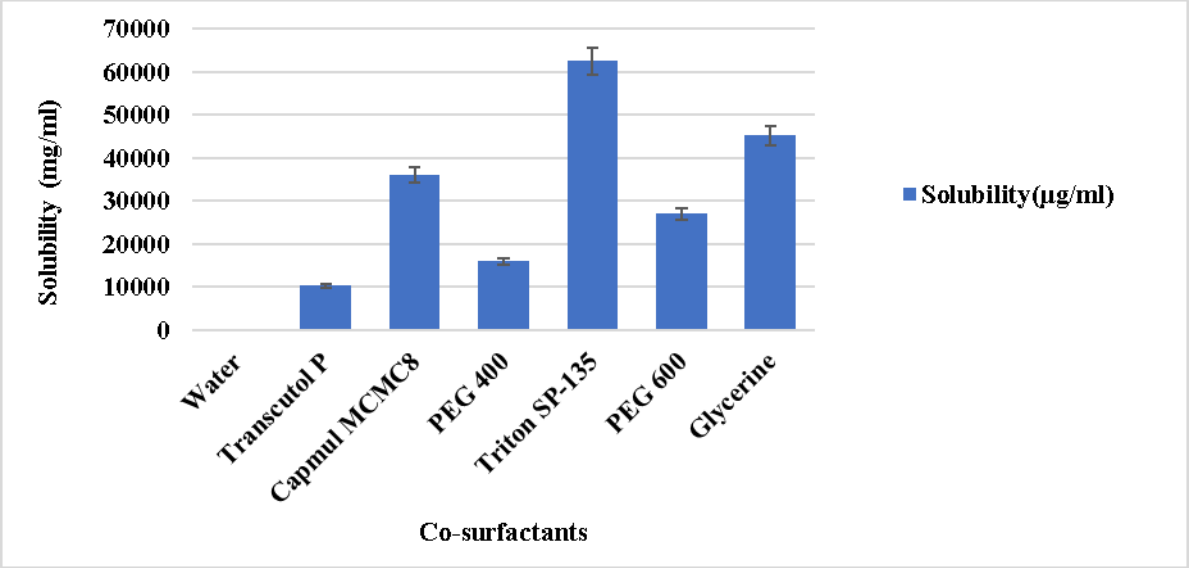


Figure 3. Solubility of Nifedipine in various Co- Surfactants



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. Sesame oil - Labrasol -Triton SP-135 system with Smix ratio in 3:1 exhibited larger nanoemulsification region (Fig.ure 6) as compared to 1:1 and 2:1 Smix ratio (Figure 4 and 5).

Figure 4.. Ternary phase diagram for Sesame oil - Labrasol -Triton SP-135 with Smix in 1:1 ratio (Key: the filled region within the ternary phase diagram indicates nanoemulsification area where the transmittance is greater than 90)

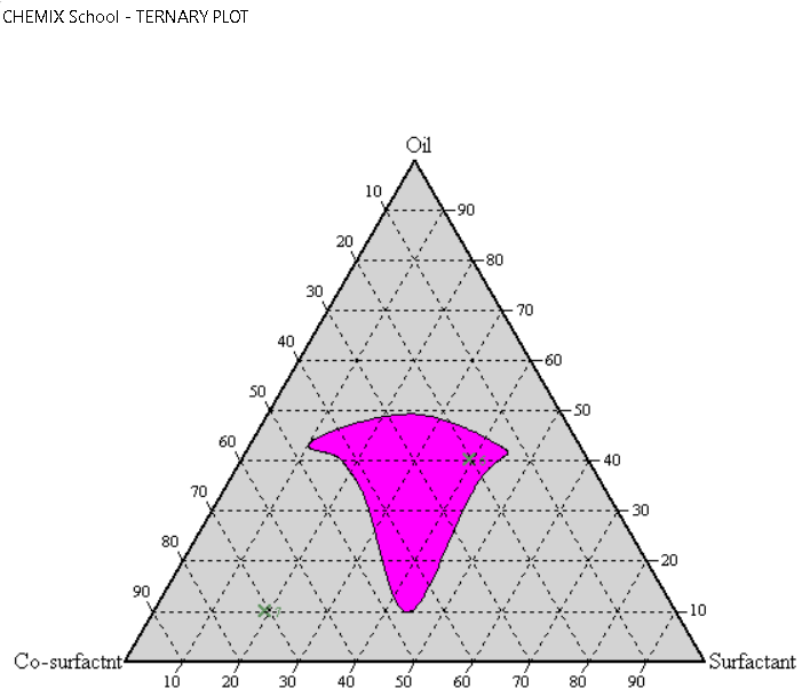


Figure 5. Ternary phase diagram for Sesame oil - Labrasol -Triton SP-135 with Smix in 2:1 ratio (Key: the filled region within the ternary phase diagram indicates nanoemulsification area where the transmittance is greater than 90)

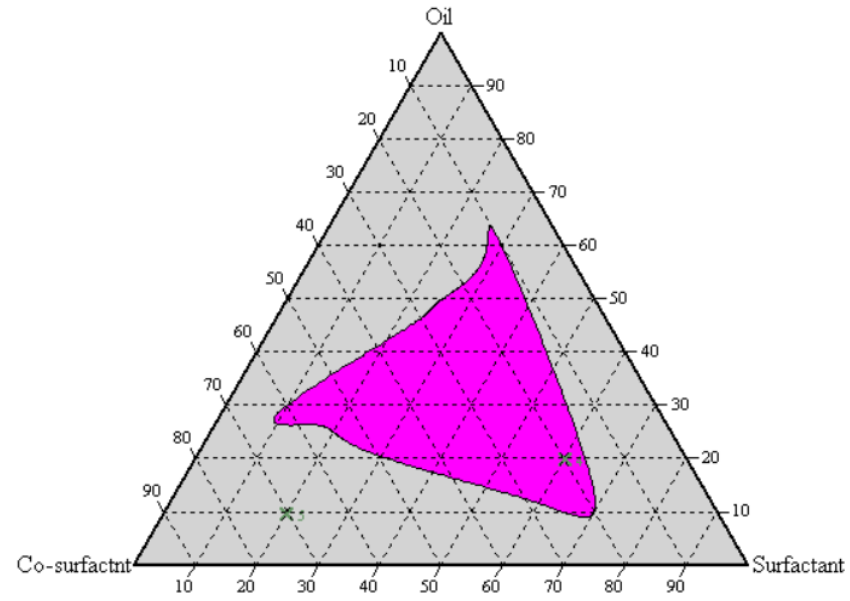


Figure 6. Ternary phase diagram for Sesame oil - Labrasol -Triton SP-135 with Smix in 3:1 ratio (Key: the filled region within the ternary phase diagram indicates nanoemulsification area where the transmittance is greater than 90)

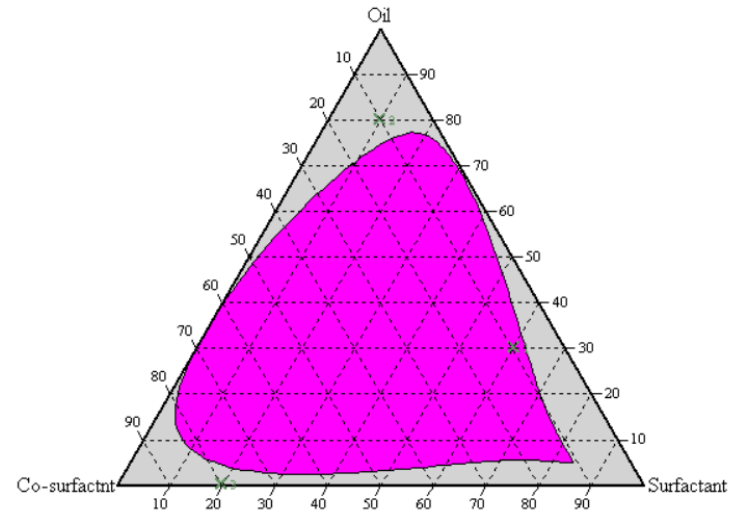


Figure 7. Ternary phase diagram for 30 mg of Nifedipine loaded in Sesame oil - Labrasol -Triton SP-135 system with Smix in 3:1 ratio (Key: the filled region within the ternary phase diagram indicates nanoemulsification area where the transmittance is greater than 90)

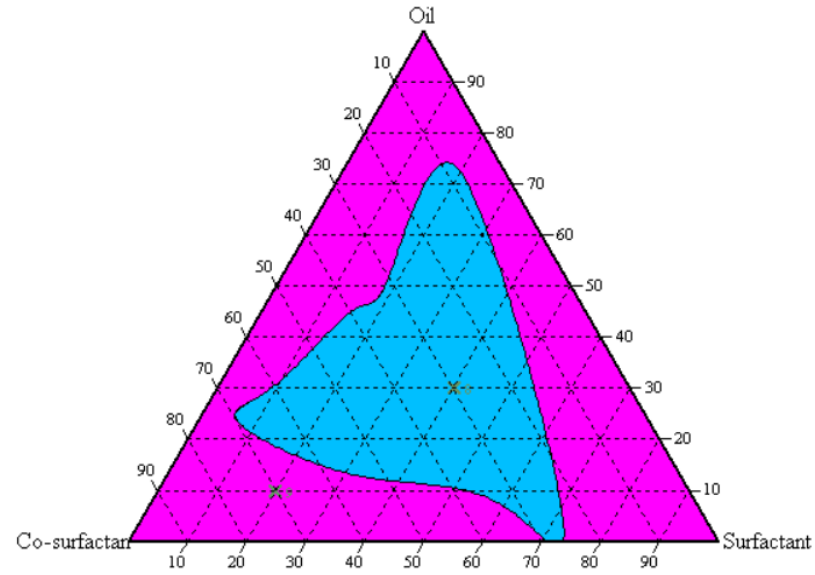


Figure 8. Ternary phase diagram for 60 mg of Nifedipine loaded in Sesame oil - Labrasol -Triton SP-135 system with Smix in 3:1 ratio (Key: the filled region within the ternary phase diagram indicates nanoemulsification area where the transmittance is greater than 90).

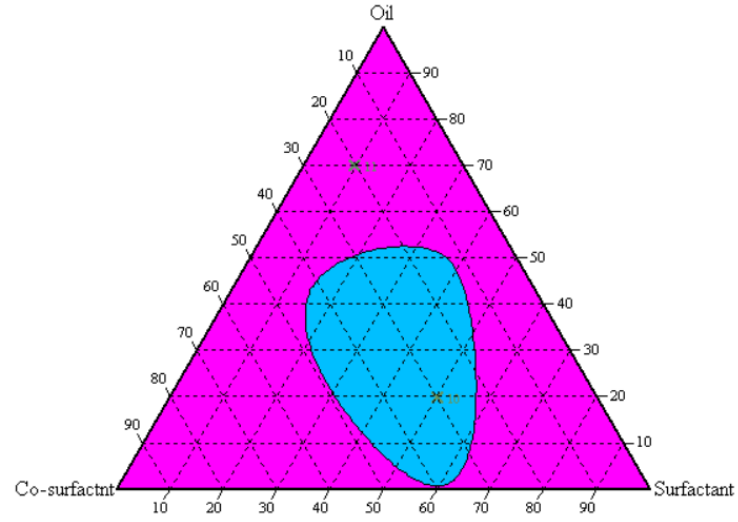
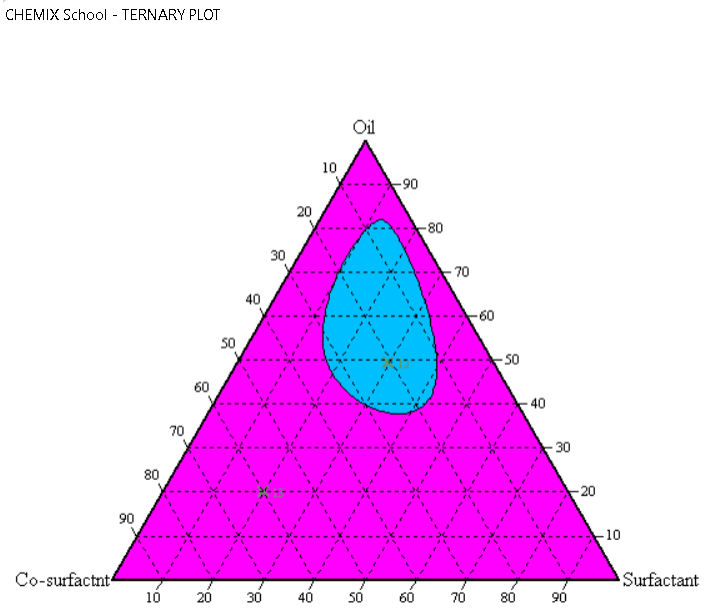


Figure 9. Ternary phase diagram for 90 mg of Nifedipine loaded in Sesame oil - Labrasol -Triton SP-135 system with Smix in 3:1 ratio (Key: the filled region within the ternary phase diagram indicates nanoemulsification area where the transmittance is greater than 90)



The mean globule size was decreased with increase in surfactant concentration. Hence the systems containing Sesame oil - Labrasol -Triton SP-135 with 3:1 Smix 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.

Effect of nifedipine loading

Incorporation of Nifedipine (30 mg, 60 mg and 90 mg) led to a considerable decrease in transmittance values (figure 9, 10 and 11). The area of nanoemulsification was considerably reduced with increase in nifedipine loading in to the Sesame oil - Labrasol -Triton SP-135 system with 3:1 Smix ratio (figure11) hence for the stability reasons of the SNEDDS, system containing 30 mg of nifedipine was chosen (figure 9) for formulation of nifedipine SNEDDS and further studies.

Figure 10. comparative dissolution profile of Nifedipine pure drug and Nifedipine SNEDDS formulation (F1-F15)

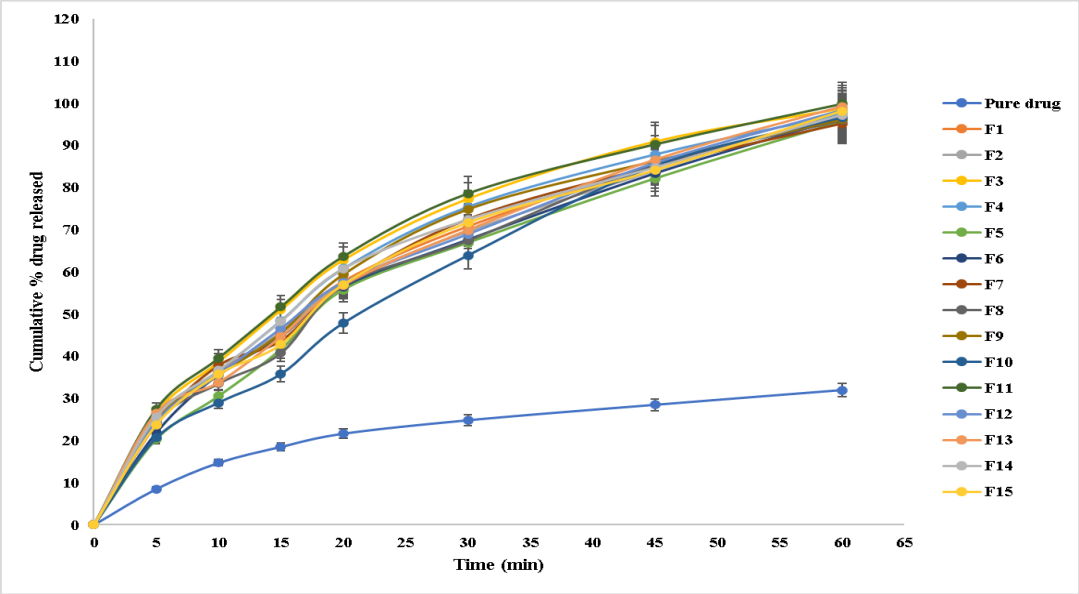
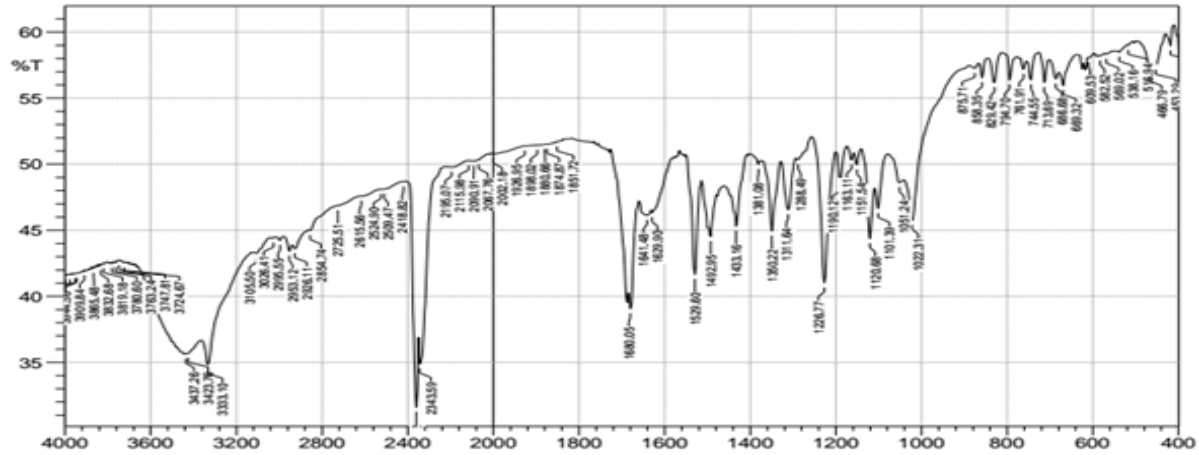


Figure 11. FTIR spectrum of Nifedipine pure drug



Preparation and Evaluation of Nifedipine SNEDDS

From the above results it was found that sesame oil concentration in the range of 20-73% w/w, Labrasol in the range of 20-60% w/w and triton SP-135 in the range of 5-20% w/w in 3:1 of oil: Smix ratio with 30mg of loaded Nifedipine drug produced the SNEDDS having the transmittance greater than 90, with good stability.

Visual Observations

Visual observations indicated that at higher levels of surfactant, the spontaneity of the self-emulsification process was increased. This may be due to excess penetration of water into the bulk oil causing massive interfacial disruption and ejection of droplets into the bulk of aqueous phase (Pouton, C.W.et al, 1997). When a co-surfactant, triton SP-135 was added to the system, it further lowered the

interfacial tension between the o/w interfaces and also influenced the interfacial film curvature (Table 2).

Table 2. Visual observation and turbidity measurement values

Formulation code	Visual Observation	Turbidity (NTU)
F1	A	18.86
F2	A	17.52
F3	A	16.75
F4	A	17.84
F5	A	21.79
F6	A	19.91
F7	A	22.11
F8	B	21.03
F9	B	20.64
F10	A	19.57
F11	A	15.84
F12	B	17.01
F13	B	16.24
F14	B	18.41
F15	B	17.30

Turbidity Measurement

Turbidity values (NTU) have been reported to be of use in SNEDDS characterization (Nazzal, S. et al, 2002) 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 1min, hence it gives a good correlation between transmittance and turbidity values (table 2).

Robustness to Dilution

Nanoemulsions resulting from the dispersion of nifedipine 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 96.25±1.84 to 99.88±1.38% with maximum value exhibited by F11 (Table 3). The entrapment efficiency of all formulations varies between 95.61±1.40to 98.74±1.63% with maximum value displayed by F11 (Table 3).

Table 3. % drug content and % entrapment efficiency values

Formulation code	Drug content (%)	% Entrapment Efficiency
F1	97.62±1.25	96.81±1.31
F2	98.41±1.19	97.43±1.64
F3	99.13±1.58	98.09±1.15
F4	98.20±1.74	97.27±1.84
F5	96.67±1.47	95.82±1.83
F6	97.09±1.37	96.39±1.48
F7	96.25±1.84	95.61±1.40
F8	96.86±1.36	96.02±1.38
F9	96.94±1.94	96.11±1.28
F10	97.24±1.45	95.52±1.73
F11	99.88±1.38	98.74±1.63
F12	98.89±1.75	97.92±1.53
F13	99.41±1.47	98.45±1.73
F14	97.87±1.68	97.07±1.83
F15	98.69±1.49	97.72±1.38

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

In Vitro Dissolution Tests

Faster release rates were observed for nifedipine SNEDDS than the pure drug. All Nifedipine SNEDDS formulations (F1-F15) completed dissolution within 60 min and all formulation released more than 95% of drug, whereas, pure drug released 31.92±0.27in 60min. Formulation F11 exhibited highest drug release of 99.86±0.78% within 30min. The release of the drug from SNEDDS formulation was increased proportionally with increase in surfactant concentration and hence F11 exhibited high drug release (Figure 14).

Figure 12. FTIR spectrum of Sesame oil

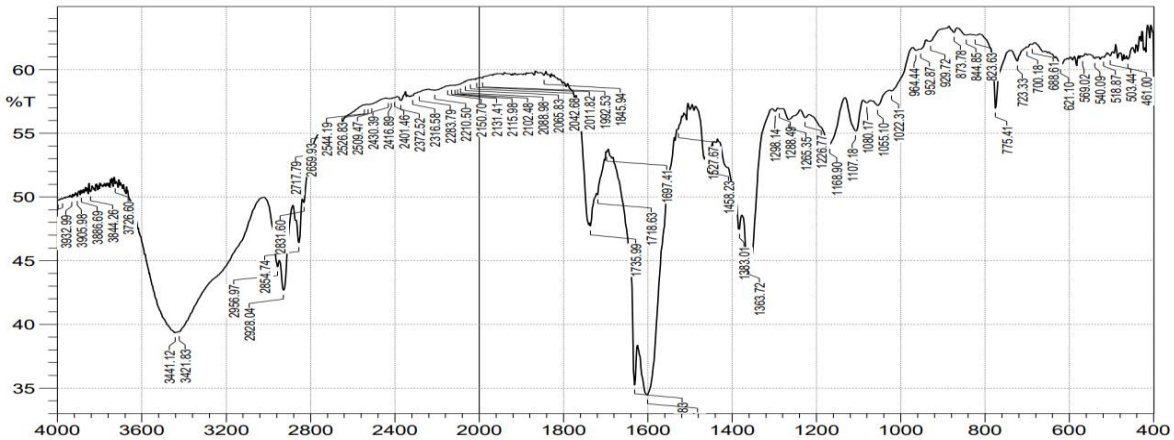


Figure 13. FTIR spectrum of labrasol surfactant

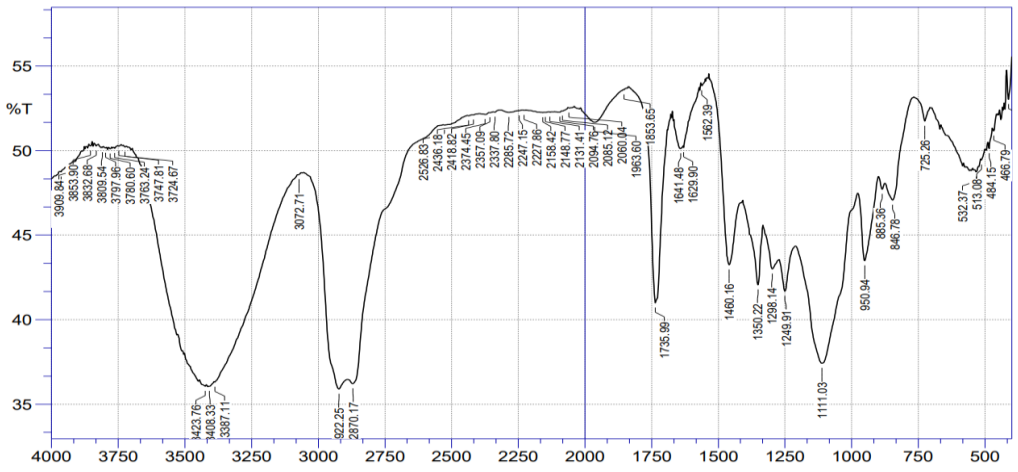


Figure 14. FTIR spectrum of Triton-SP-135 Co-surfactant

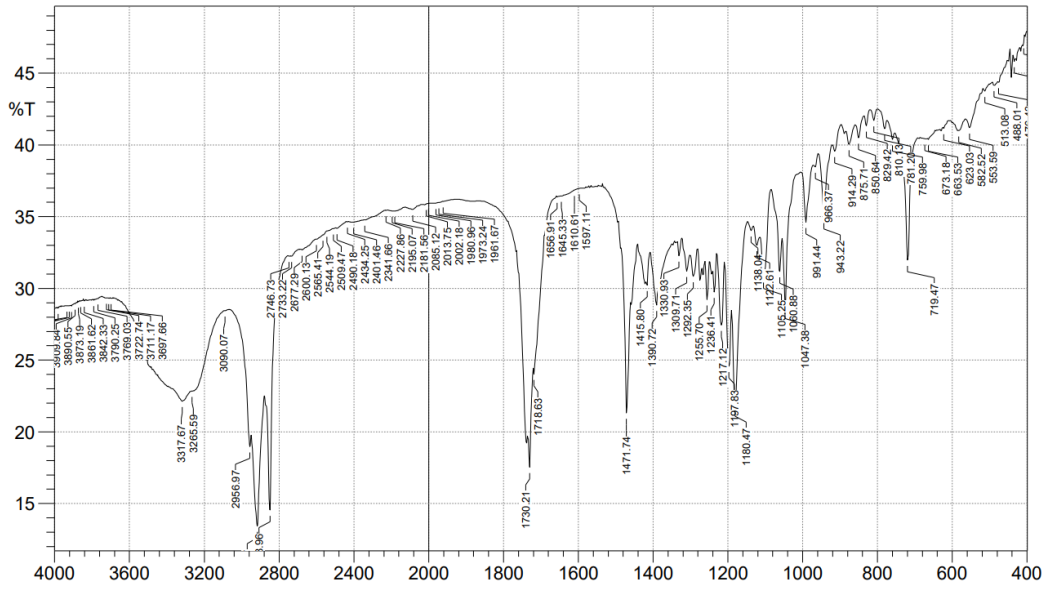


Figure 15. FTIR spectrum of optimised formulation of nifedipine SNEDDS formulation (F11)

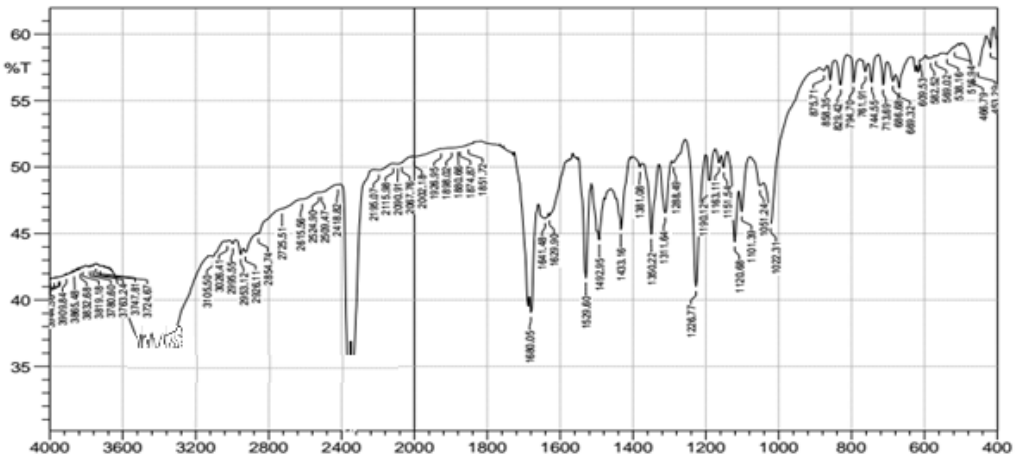


Figure 16. Particle size of optimised SNEDDS formulation of Nifedipine (F11)

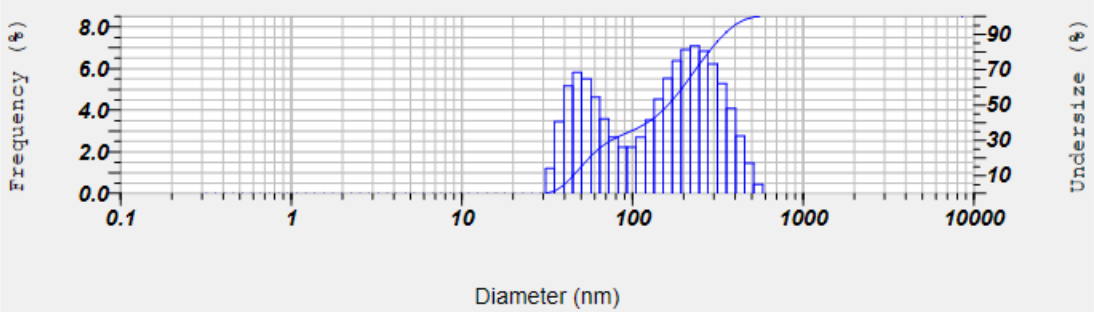


Figure 17. Zeta potential of optimised SNEDDS formulation of Nifedipine (F11)

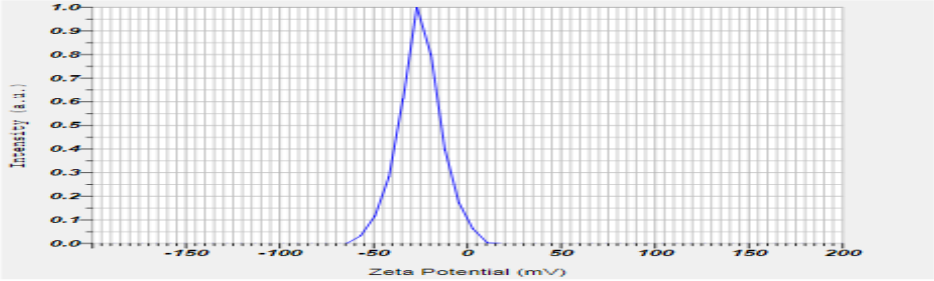
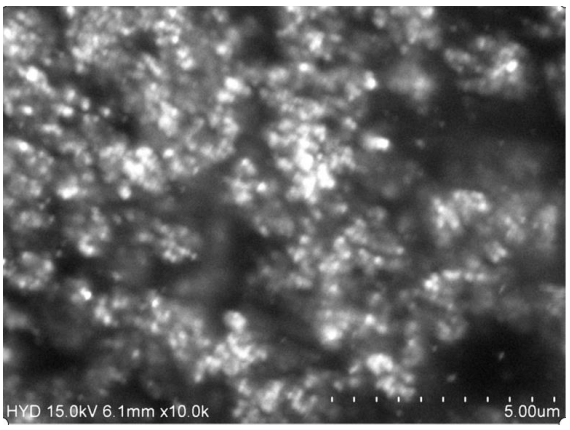
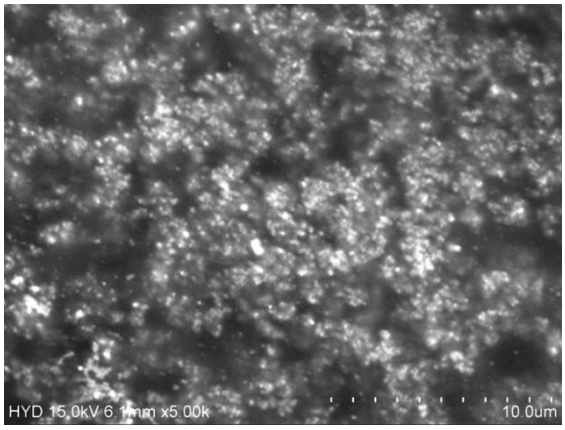


Figure 18. SEM images of optimised formulation of Nifedipine SNEDDS F11 (A and B)



(18A)



(18B)

Characterization of optimised formulation

FTIR Spectroscopy

The FTIR spectrum of Nifedipine showed several characteristic peaks as shown in Fig. 11 and it had characteristic peak of the N-H stretching vibration at 3333.10 cm−1, 3105.50 cm^{-1} (aromatic group) - vAr-H (-CH) bands, 1680.05 cm^{-1} (aryl carboxylic group) - ν (C=O) stretching vibration, 1629.90 cm^{-1} (pyridine group) - ring breathing band and 1226.77 cm^{-1} (carbonyl group) – ν C-O/ δ O-H and a band of peaks between 1800–1000 cm−1, with the main peak at 1641.48 cm−1 indicative of the C=O stretch of the ester group. the peaks in the FT-IR spectra are sharp indicating the crystalline nature of nifedipine and this is confirmed in the other studies. The FTIR spectra of optimized SNEDDS formulation (Figure 19) were having similar fundamental peaks and pattern, hence, there was no major interaction between the drug and excipients used in the study. (Figures 12, 13, 14 and 15)

Globule size and zeta potential

The mean globule size of F11 was 172.3nm indicating nanoparticle range that facilitates absorption. The zeta potential (mean) values of SNEDDS formulations were found to be in between -24.7 mV. The zeta potential value > 5 mV provide an excellent stability (Figure 16, 17 and 18). (Kang, B. Ket al, 2004).

SEM studies

Morphological and structural examination of the optimized batch F11 of Nifedipine loaded SNEDDS was carried out using transmission electron microscope. These results were in accordance to that of globule size analysisand was observed that the size of all droplets of SNEDDS F11 was less than 200 nm as furnished in Figure 18A and 18B. However, the shape of droplets was found to be spherical.

Forced Degradation and Accelerated Stability Studies of Optimized SNEDDS

Forced degradation and accelerated stability studies were conducted in order to know the stability of nifedipine in the gastric environment and in SNEDDS formulation.

Forced Degradation Studies

Stability of nifedipine from nifedipine SNEDDS in the gastro intestinal environment was assessed by conducting forced degradation studies (acid, alkali and neutral degradation) and compared with pure drug (Table 4). Optimized nifedipine SNEDDS, pure drug showed no degradation even after 24 hours storage in methanol, distilled water and pH 6.8 phosphate buffer. Pure drug present in 0.1N HCl solution showed 26.65% degradation within 4 hours and the degradation was increased with time (71.53% degradation was found at 24th hour). Nifedipine showed very less decomposition (<1% degradation) for up to 4 hours and then decomposed with the time in 0.1N HCl solution. Nifedipine showed 0.04, 16.02, 26.02 and 34.09% degradation in 4th, 6th, 12th and 24th hour respectively. The degradation of nifedipine from optimised nifedipine SNEDDS formulation was significantly less when compared to the pure drug degradation.

Table 4. Percent degradation of nifedipine from pure drug and optimized nifedipine SNEDDS in forced degradation study

Formulation code	Time (hr) / Diluting Solvent	%Drug Degraded (%, mean ± s.d, n=3)				
		0 Hour	4th Hour	6th Hour	12th Hour	24th Hour
Pure drug	Methanol	0.01 ± 0.62	0.02 ± 1.22	0.01 ± 1.02	0.010±0.22	0.11 ± 1.75
	Water	0.02 ± 1.42	0.01 ± 1.66	0.02 ± 0.41	0.02 ± 1.71	0.01 ± 1.01
	0.1 N HCl	0.06 ± 1.31	26.65 ± 1.12	28.02 ± 0.41	41.95± 1.49	71.02 ± 1.19
	pH 6.8 phosphate Buffer	0.01 ± 0.44	0.02 ± 1.05	0.02 ± 1.69	0.04 ± 1.78	0.06 ± 1.88
F11	Methanol	0.02 ± 1.14	0.16± 0.55	0.15 ± 1.28	0.01± 1.07	0.02 ± 1.16
	Water	0.01 ± 1.95	0.25 ± 1.45	0.02 ± 1.74	0.12 ± 1.21	0.08 ± 1.18
	0.1 N HCl	0.01 ± 1.65	0.04 ± 1.75	16.02 ± 1.28	26.02 ± 0.65	34.09 ± 1.24
	pH 6.8 phosphate Buffer	0.01 ± 1.77	0.06 ± 0.82	0.08 ± 1.15	0.02 ± 1.32	0.12 ± 1.52

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

Accelerated Stability Studies

No visible physical changes were observed in all the formulations withdrawn from the humidity chambers. The samples were assayed for %entrapment efficiency, % drug content and in-vitro drug release and the results are shown in Table 5. No significant difference was observed after storage at accelerated conditions at 40±2° C/75±5% RH for a period of six months.

Table 5. Storage at 40±2° C/75±5% RH for 6 Months.

Retest time for optimized formulation F11	% Drug content	% Entrapment efficiency	In-vitro drug release (%)
0 days	99.88±1.38	98.74±1.63	99.86±0.78
30 days	99.42±0.53	98.56±0.74	99.22±1.46
60 days	99.23±0.46	98.32±0.19	98.83±1.19
90 days	99.09±0.83	98.12±0.67	98.65±1.01

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

Conclusion

The present study the nifedipine SNEDDS were prepared using sesame as an oil, labrasol as a surfactant, and triton SP-135 as a co-surfactant optimized using ternary phase diagram. At physical evaluation, SNEDDS optimum values obtained involved drug loading of 30 mg of drug SNEDDS, turbidity of 15.84 NTU, % drug content of 99.88%, particle size 172.3 nm, zeta potential of -24.7 mV, and stability for 6 months. The compatibility study carried out by comparing FTIR spectra of pure drug and optimised formulation. In vitro drug dissolution values obtained at 60 min was 99.86% with minimized pH dependent degradation when compared to pure drug. Hence a highly soluble SNEDDS formulation of nifedipine was developed with enhanced stability and dissolution rates.

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