International Journal of Scientific Research and Engineering Development-– Volume 5 Issue 3, May-June 2022

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RESEARCH ARTICLE OPEN ACCESS

# Development of Lipid-Based Nano Emulsions of Poorly Soluble Drug Nebivolol

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## Abstract

The main purpose of this study was to investigate the potential of self-nano emulsified drug delivery system (SNEDDS) to improve the solubility and dissolution of nebivolol. SNEDDS was developed by using rational blends of excipients with good solubilizing ability for nebivolol which was selected based on solubility studies. Further phase diagrams were constructed to determine the self-emulsifying region. The SNEDDS formulations were evaluated for various tests and characterised for FTIR, DSC, SEM and stability studies. The optimal formulation (F14) with the best self-nano emulsified and solubilization ability consisted of 25% (w/w) corn oil as oil, 57% (w/w) caproic acid as surfactant and 18% (w/w) PEG600 as cosurfactant. The formulation displayed maximum drug content of 99.23%, 98.51% entrapment efficiency and drug release of 99.96% in 60 minutes. The average droplet size and zeta-potential of the optimal SNEDDS were 165.2 nm and -13.2 mv, respectively. The forced degradation study results show that the pH dependant degradation and the formulation F14 found to be stable after storage at accelerated conditions at 40±2° C/75±5% RH for a period of six months. Hence SNEDDS may be considered as suitable formulation approach for improving the solubility, dissolution and therapeutic efficiency of nebivolol.

*Keywords:* Nebivolol, Hypertension, Self-nanoemulsified drug delivery system, Pseudoternary phase diagram, in-vitro drug release, Forced degradation studies

## I. INTRODUCTION

Nanotechnology has become a buzzword for scientific experts, and efforts are ongoing to extend its applications in various medical and pharmaceutical aspects. The nanoscale technologies can be generally categorized into lipid-based nanocarriers, polymeric nanocarriers, inorganic nanocarriers, and drug nanoparticles or nanosuspensions. Within the lipid-based nanocarriers category, there has been a resurgence of interest in nanoemulsions since low-energy emulsification methods, such as spontaneous or self-nanoemulsification, have been developed. Self-nanoemulsifying drug delivery systems (SNEDDS) are anhydrous homogeneous liquid mixtures, composed of oil, surfactant, drug, and/or cosolvents, which spontaneously form transparent nanoemulsion

(20–200 nm droplet size) upon aqueous dilution with gentle agitation [1], [2].

A vital feature of a successful SNEDDS formulation is its capability to hold the drug in solution, throughout the GIT, for sufficient time to allow for absorption. Many poorly water-soluble drugs have high solubility in SNEDDS formulations but could make a risk of precipitation after aqueous dispersion of the formulation or during its digestion in the intestine [3]

The model drug for the current study had been selected from the biopharmaceutical classification system class II. Nebivolol hydrochloride is chemically known as α, α- [iminobis (methylene)] bis [6-flouro3,4-dihydro-2H-1-benzopyran-2-methanol] hydrochloride. It is a highly selective β1-blocker with nitric oxide mediated vasodilatory actions and beneficial effects on vascular endothelial function. Nebivolol is used in the management of hypertension. It is given by mouth as the hydrochloride although doses are expressed in terms of base. The usual dose is 10 mg and 5 mg daily. An initial dose of 2.5 mg daily is employed in the elderly and in patients with renal impairment [4]. The main objective of this work was to investigate the possibility of improving the solubility and dissolution rate of Nebivolol by developing suitable SNEDDS.

## II. MATERIAL AND METHODS

### *A. Materials used*

Nebivolol 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, propylene glycol, capmul MCMC8, PEG 400 and PEG 600 were purchased from Gattefosse, Mumbai. All the reagents used were of analytical grade.

### *B. Methods*

#### *1) Solubility of nebivolol in Vehicles*

Naturally occurring different vegetable oils, various surfactants and co-surfactants were studied for nebivolol solubility in order to identify the components for construction of ternary phase diagrams procedure as reported elsewhere. Supernatant was analyzed for nebivolol using UV spectrophotometer at 280nm**.** [5]

#### *2) 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. The ratios with no phase separation and clear appearance with no turbidity were separated and checked for the transmittance using UV spectrophotometer [6]. The transmittance value more than 90 indicated nano size droplets formation hence these ratios were noted and used for plotting pseudo-ternary phase diagram [7] Pseudo ternary phase diagram is constructed using CHEMIX software.

#### *3) Effect of nebivolol loading*

In the view of this, effect of nebivolol loading on the transmittance, phase behaviour and area of nanoemulsion formation was studied on Corn oil - Caproic acid - PEG600 compositions with Smix in 3:1 ratio, which gave more area of nanoemulsification region among the other ratios.

Fifteen compositions of varying ratios of Corn oil - Caproic acid - PEG600 were taken and in 1ml composition of each ratio were incorporated with 2.5 mg, 5 mg and 10 mg of nebivolol (i.e., 15*3=45 formulations). [8]

#### *4) Preparation and Evaluation of Nebivolol SNEDDS*

A series of SNEDDS (F1- F14, the composition was shown in Table 1) which showed transmittance values more than 90) were selected from 5 mg loaded nebivolol system and prepared as described above [7]. About 1ml of the formulation (equivalent to 5 mg of the nebivolol) 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, and robustness to dilution and in vitro dissolution study and were optimized [9]

. TABLE 1: COMPOSITION OF NEBIVOLOL SNEDDS

| S. No | Formulation code | Nebivolol drug (mg) | Ratios of Oil: Smix | Oil (Corn oil) | Smix 3:1 | |
|---|---|---|---|---|---|---|
| | | | | | Surfactant (Caproic acid) | Co-surfactant (PEG 600) |
| 1 | F1 | 10 | 01:01 | 50 | 37.5 | 12.5 |
| 2 | F2 | 10 | 01:02 | 33 | 49.5 | 16.5 |
| 3 | F3 | 10 | 02:01 | 66 | 24.75 | 8.25 |
| 4 | F4 | 10 | 03:01 | 75 | 18.75 | 6.25 |
| 5 | F5 | 10 | 02:03 | 40 | 45 | 15 |
| 6 | F6 | 10 | 02:05 | 28.5 | 53.25 | 17.75 |
| 7 | F7 | 10 | 03:02 | 60 | 30 | 10 |
| 8 | F8 | 10 | 03:04 | 42.6 | 42.6 | 14.8 |
| 9 | F9 | 10 | 03:07 | 30 | 52.5 | 17.5 |
| 10 | F10 | 10 | 04:03 | 57.1 | 31.95 | 10.65 |
| 11 | F11 | 10 | 05:02 | 71 | 21.3 | 7.1 |
| 12 | F12 | 10 | 05:03 | 62.5 | 28.12 | 9.3 |
| 13 | F13 | 10 | 07:03 | 70 | 22.5 | 7.5 |
| 14 | F14 | 10 | 01:03 | 25 | 56.25 | 18.75 |

### *C. Evaluations*

Visual Observations, Turbidity Measurement, Robustness to Dilution, Percentage drug content, Entrapment efficiency**.** [10], [11].

### D. In Vitro Dissolution Study

*In vitro* dissolution studies were conducted for nebivolol pure drug and nebivolol SNEDDS formulations (F1-F14) was performed using USP dissolution Apparatus II (Lab India DS 8000, Mumbai, India). Hard gelatin capsules, size "1" filled with nebivolol 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. The samples were suitably diluted and analyzed for nebivolol using UV method spectrophotometrically at 280nm [13], [13]. For comparison, similarly dissolution studies of pure drug were also performed [14]. All measurements were done in triplicate [15].

### *E. Characterization of optimised nebivolol SNEDDS formulation*

FTIR studies, Globule Size and Zeta potential [7], Scanning electron microscopy [16]

### *F. Forced Degradation and Accelerated Stability Studies*

Nebivolol is very susceptible to decomposition when it is exposed to oxygen, light, temperature, humidity, carbon dioxide and acidic pharmaceutical excipients. The percentage degradation of nebivolol was calculated (ICH Harmonized Tripartite guideline on "*Stability Testing of New Drug Substances and Products Q1A (R2)*", 6 February**2003**). [17]

### G. *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 6 months.

## III. RESULTS AND DISCUSSION

### H. *Determination of nebivolol solubility in various excipients*

Corn oil was selected as oil phase due to its higher solubilization (3.05±0.69mg/g) of nebivolol compared to other oils (Figure 1).

Surfactant Caproic acid and co-surfactant PEG600 was selected for further studies due to their higher solubilizing capacity towards nebivolol [18], [19], [20] (Figure 2 and 3).

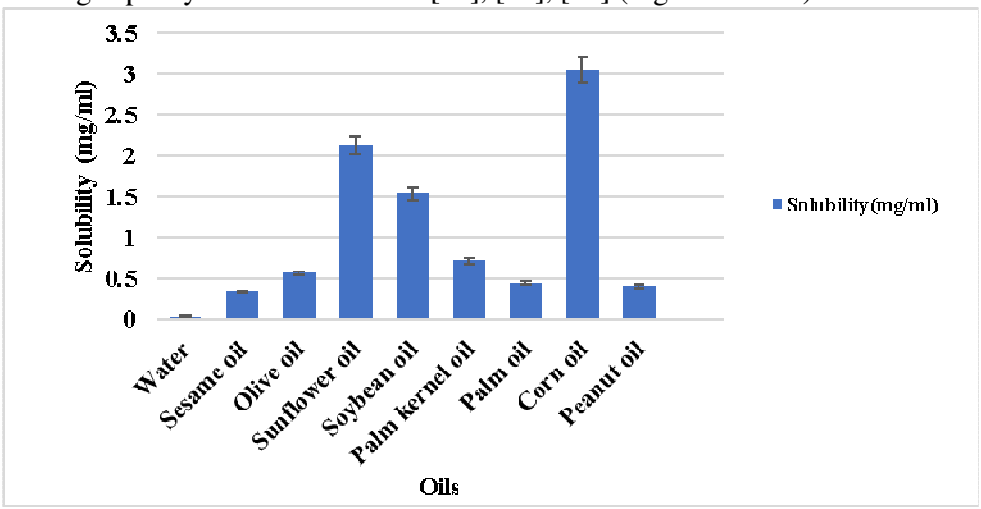



**Fig 1: solubility of nebivolol in various Oils**

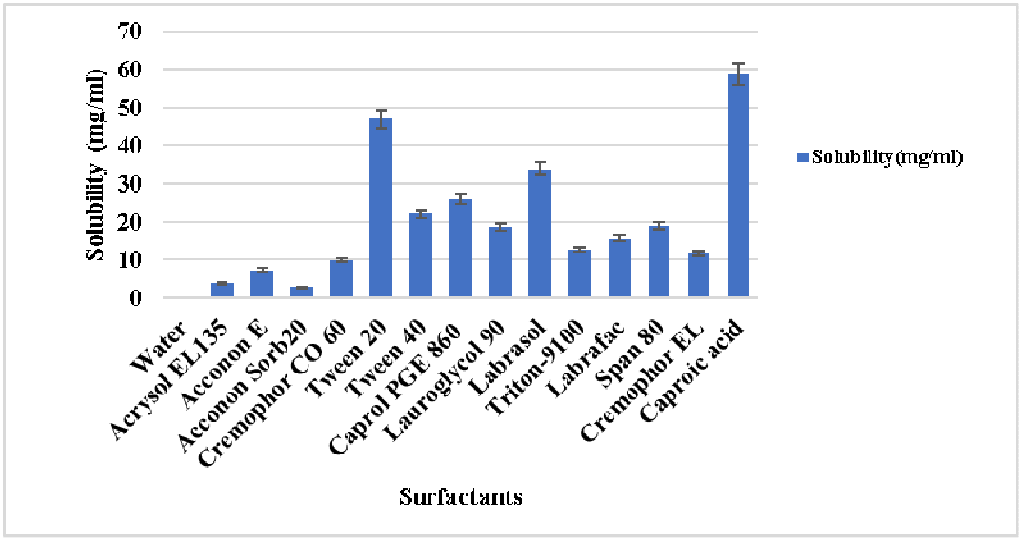



**Fig 2: solubility of nebivolol in various Surfactants**

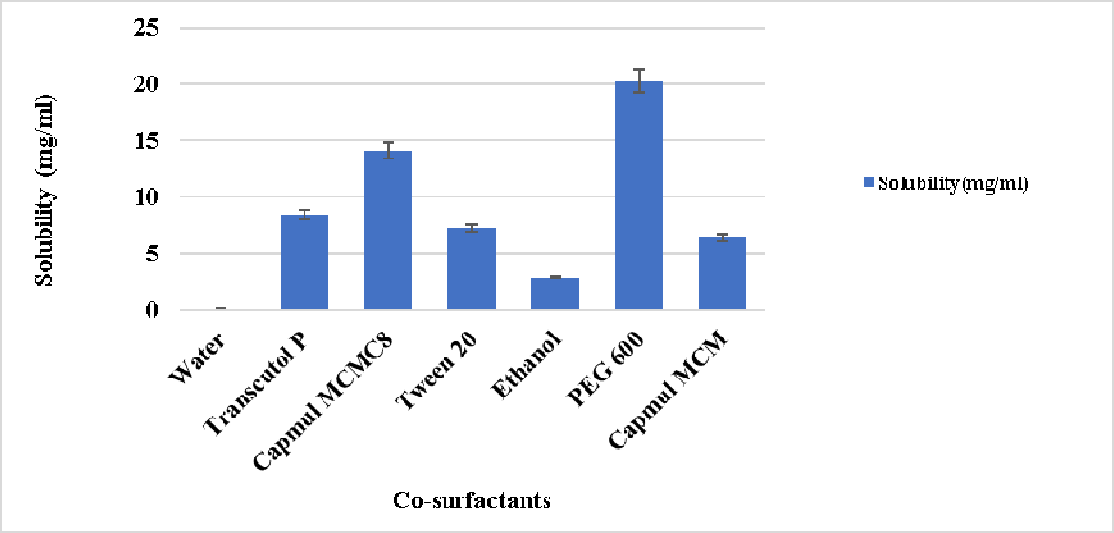



**Fig 3: Solubility of nebivolol in various Co-Surfactants**

### *I. 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. Corn oil - Caproic acid - PEG600 system with Smix ratio in 3:1 exhibited larger nanoemulsification region (Fig. **6**) as compared to 1:1 and 2:1 Smix ratio (Fig. 4 and 5).

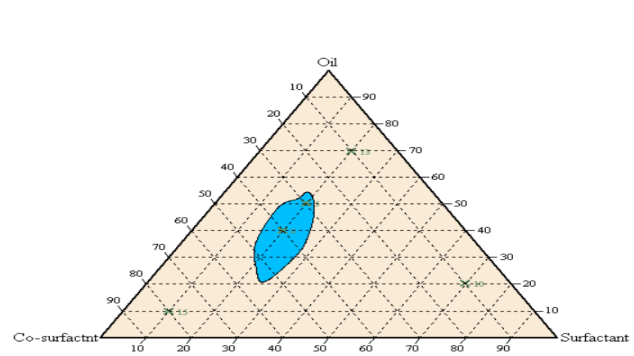



**Fig. (4).** Ternary phase diagram for Corn oil - Caproic acid - PEG600 with Smix in 1:1 ratio (Key: the filled region within the ternary phase diagram indicates nanoemulsification area where the transmittance is greater than 90)

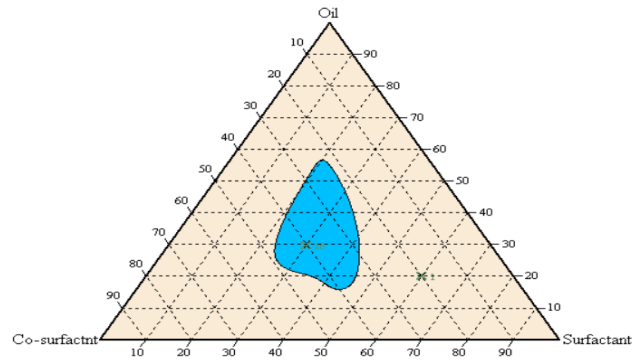



**Fig. (5).** Ternary phase diagram for Corn oil - Caproic acid - PEG600 with Smix in 2:1 ratio (Key: the filled region within the ternary phase diagram indicates nanoemulsification area where the transmittance is greater than 90).

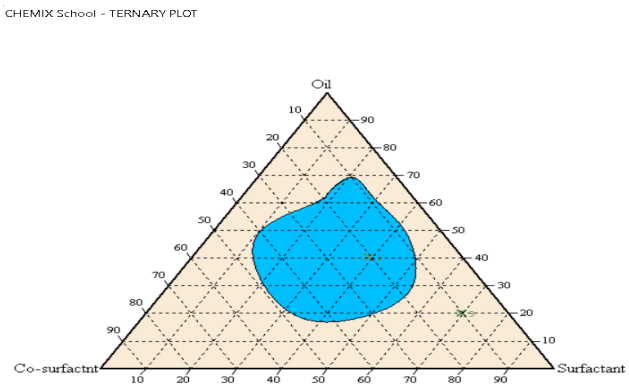



**Fig. (6).** Ternary phase diagram for Corn oil - Caproic acid - PEG600 with Smix in 3:1 ratio (Key: the filled region within the ternary phase diagram indicates nanoemulsification area where the transmittance is greater than 90).

The mean globule size was decreased with increase in surfactant concentration. Hence the systems containing Corn oil - Caproic acid - PEG600 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.

### *J. Effect of nebivolol loading*

Incorporation of nebivolol (2.5 mg, 5 mg and 10 mg) led to a considerable decrease in transmittance values (figure 7, 8 and 9). This behaviour could be thought that undissolved drug in the compositions affected the clarity and thereby transmittance value to decrease with increased nebivolol amount. Oil globules were observed on the surface after dispersion on standing for majority of the compositions containing high nebivolol. The area of nano emulsification was considerably reduced with increase in nebivolol loading in to the Corn oil - Caproic acid - PEG600 system with 3:1 Smix ratio hence for the stability reasons of the SNEDDS, system containing 10 mg of nebivolol was chosen for formulation of nebivolol SNEDDS and further studies.

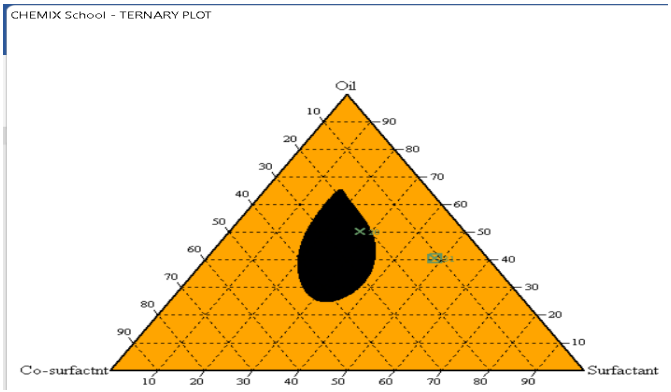



**Fig. (7).** Ternary phase diagram for 2.5 mg of nebivolol loaded in Corn oil - Caproic acid - PEG600 system with Smix in 3:1 ratio (Key: the filled region within the ternary phase diagram indicates nanoemulsification area where the transmittance is greater than 90)

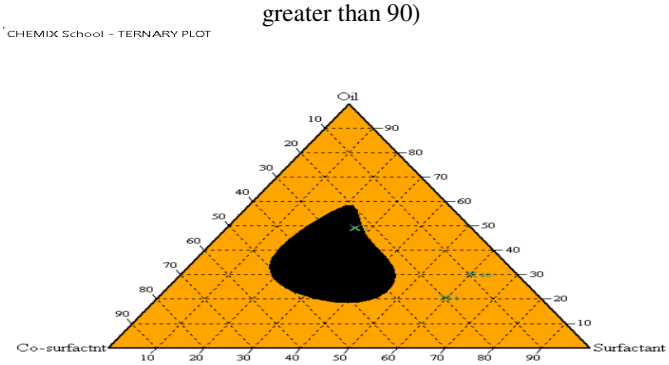



**Fig. (8).** Ternary phase diagram for 5 mg of nebivolol loaded in Corn oil - Caproic acid - PEG600 system with Smix in 3:1 ratio (Key: the filled region within the ternary phase diagram indicates nanoemulsification area where the transmittance is greater than 90)

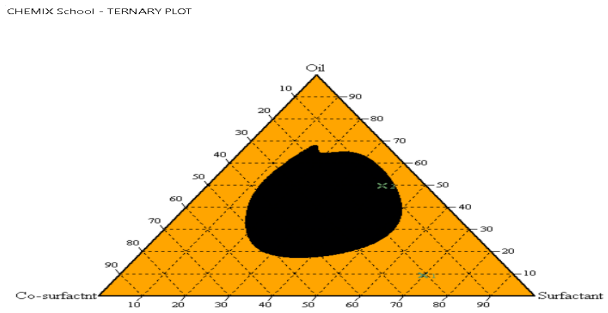



**Fig. (9).** Ternary phase diagram for 10 mg of nebivolol loaded in Corn oil - Caproic acid - PEG600 system with Smix in 3:1 ratio (Key: the filled region within the ternary phase diagram indicates nanoemulsification area where the transmittance is greater than 90).

### *K. Preparation and Evaluation of nebivolol SNEDDS*

From the above results it was found that corn oil concentration in the range of 24-75% w/w, Caproic acid in the range of 15-60% w/w and PEG 600 in the range of 5-20% w/w in 3:1 of oil: Smix ratio with 10mg loaded nebivolol drug produced the SNEDDS having the transmittance greater than 90, with good stability.

### *L. Evaluations*

#### *1) 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 [21]. When a co-surfactant, PEG 600 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).

#### *2) Turbidity Measurement*

Turbidity values (NTU) have been reported to be of use in SNEDDS characterization [22]. 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).

**TABLE 2: VISUAL OBSERVATION AND TURBIDITY MEASUREMENT VALUES**

| Formulation code | Visual Observation | Turbidity (NTU) |
|---|---|---|
| F1 | A | 16.13 |
| F2 | A | 15.11 |
| F3 | A | 17.78 |
| F4 | B | 20.48 |
| F5 | B | 15.34 |
| F6 | A | 14.69 |
| F7 | A | 16.81 |
| F8 | B | 15.72 |
| F9 | A | 14.80 |
| F10 | A | 16.54 |
| F11 | A | 19.66 |
| F12 | B | 17.22 |
| F13 | B | 18.45 |
| F14 | A | 14.19 |

*3)* ***Robustness to Dilution***

Nanoemulsions resulting from the dispersion of nebivolol SNEDDS (F1-F14) 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.

*4)* ***Percentage drug content and Entrapment efficiency***

The drug content of all formulations ranged between 95.65±0.62 to 99.23±1.14% with maximum value exhibited by F14 (table 3). The entrapment efficiency of all formulations varies between 94.32±0.92 to 98.51±1.02% with maximum value displayed by F14 (table 3).

**TABLE 3: % DRUG CONTENT AND % ENTRAPMENT EFFICIENCY VALUES**

| Formulation code | %Drug content | % Entrapment Efficiency |
|---|---|---|
| F1 | 97.90±0.65 | 97.05±1.15 |
| F2 | 98.42±1.15 | 97.91±0.51 |
| F3 | 97.23±0.14 | 96.41±1.02 |
| F4 | 95.65±0.62 | 94.32±0.92 |
| F5 | 98.30±1.19 | 97.67±1.52 |
| F6 | 99.02±1.49 | 98.25±1.77 |
| F7 | 97.75±1.78 | 96.76±1.83 |
| F8 | 98.04±1.15 | 97.31±1.29 |
| F9 | 98.85±1.66 | 98.07±1.43 |
| F10 | 97.84±1.45 | 96.98±1.95 |
| F11 | 96.71±1.13 | 96.05±1.19 |
| F12 | 97.42±1.62 | 96.54±1.25 |
| F13 | 97.11±1.89 | 96.22±1.54 |
| F14 | 99.23±0.14 | 98.51±1.02 |

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

## M. In Vitro Dissolution Tests

Faster release rates were observed for nebivolol SNEDDS than the pure drug. Nebivolol SNEDDS F1-F14 released more than 60% of drug within 30min while Pure drug released only 30.25% of drug in 60mins. Formulation F14 exhibited highest drug release of 99.96% in 60min. The release of the drug from SNEDDS formulation was increased proportionally with increase in surfactant concentration and hence F14 exhibited high drug release (Figure 10).

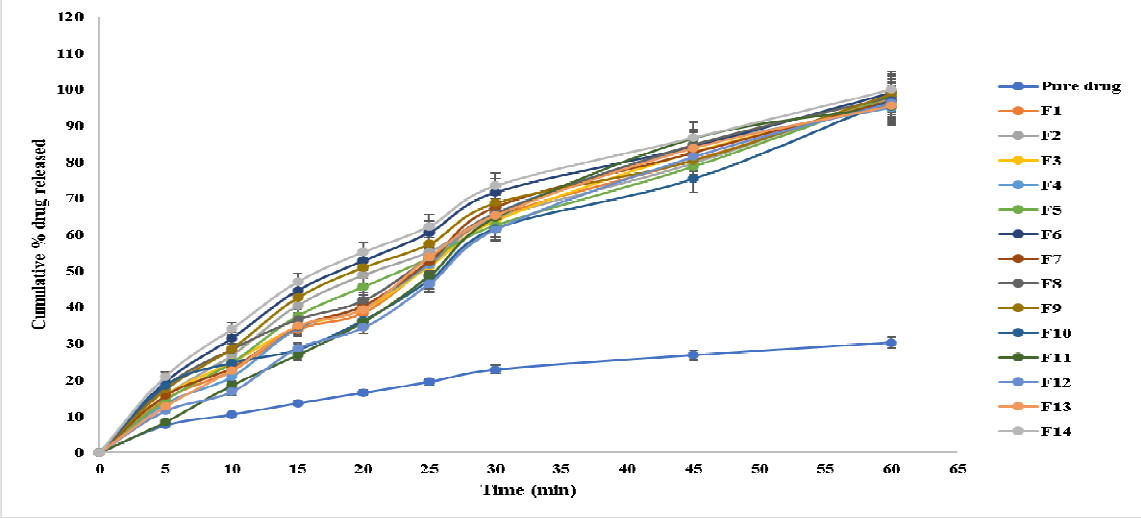



**Fig 10: Comparative dissolution profile of nebivolol pure drug and nebivolol SNEDDS formulation (F1-F14)**

## *N. Characterization of optimised formulation*

### *1) FTIR Spectroscopy:*

The characterization of pure drug nebivolol by FTIR studies was shown in fig.11. The spectrum is responsible for the presence of chemical functional groups at different frequencies. The pure Nebivolol spectrum showed the main characteristic bonds at 3201.94 $cm^{-1}$O-H stretch, 3844.26 $cm^{-1}$ (NH-bonding) 3726.60 $cm^{-1}$(OH-bonding), 1500 $cm^{-1}$C-C stretch, 1433.16 cm-1 (C-H stretching), 1141.90 $cm^{-1}$ (C-O-C stretching), 1257.63 $cm^{-1}$ C-O stretch 1074.39 $cm^{-1}$ (F-bonding), 815.92 $cm^{-1}$C-X stretch, 1141.90 $cm^{-1}$C-F stretch, 1618.33 $cm^{-}$1, a peak was found in the range of 1700–1750 cm−1 due to carboxylic acid moiety which indicates the presence of C=O stretching. The presence of prominent characteristic peaks confirming the purity of nebivolol as per the established standards. Frequencies of functional groups and unique absorption bands of pure drug remained intact in SNEDDS formulation (F14) indicate no significant interaction between drug and SNEDDS components (Figures 12, 13, 14 and 15).

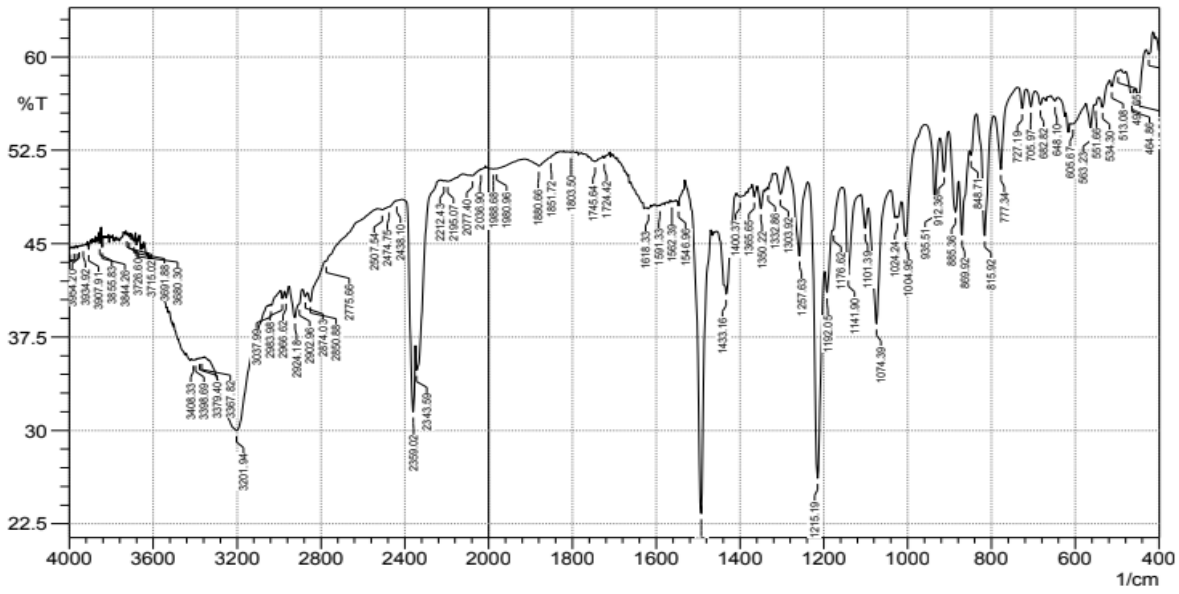



**Fig 11: FTIR spectrum of pure drug nebivolol**

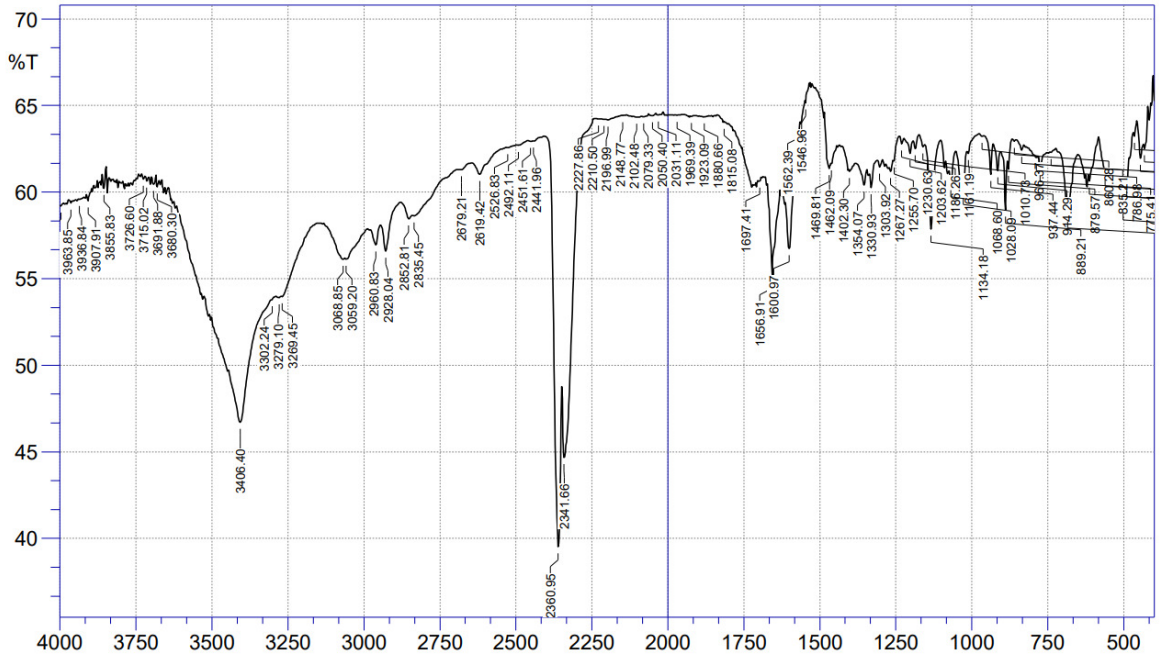



**Fig 12: FTIR spectrum of Corn oil**

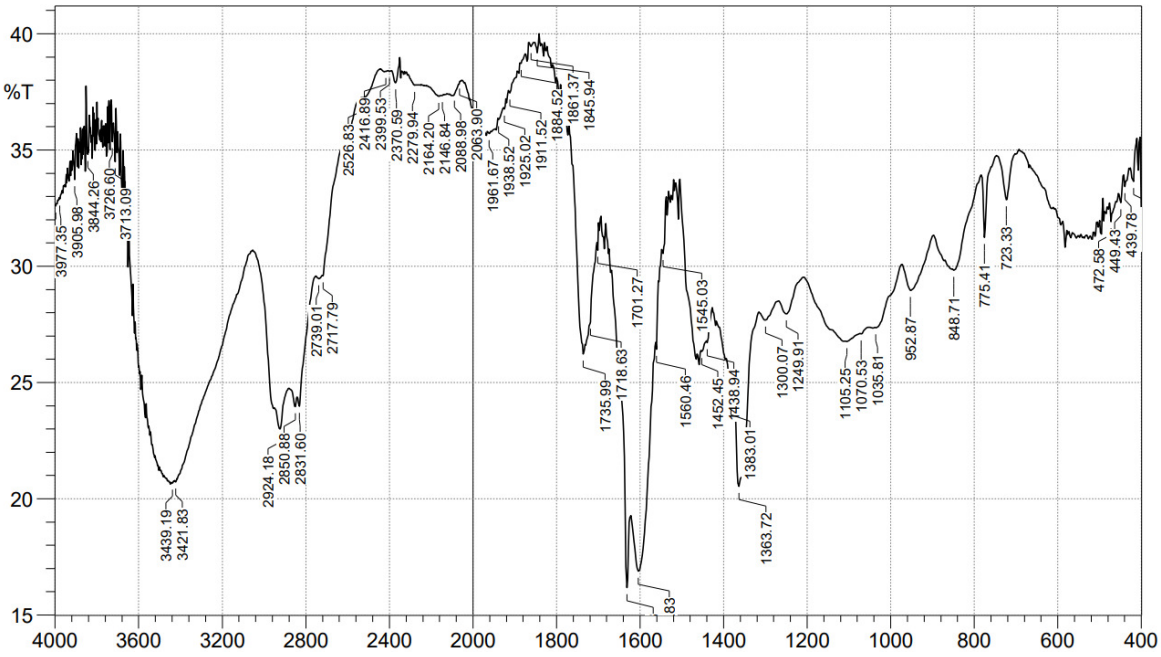



**Fig 13: FTIR spectrum of Caproic acid**

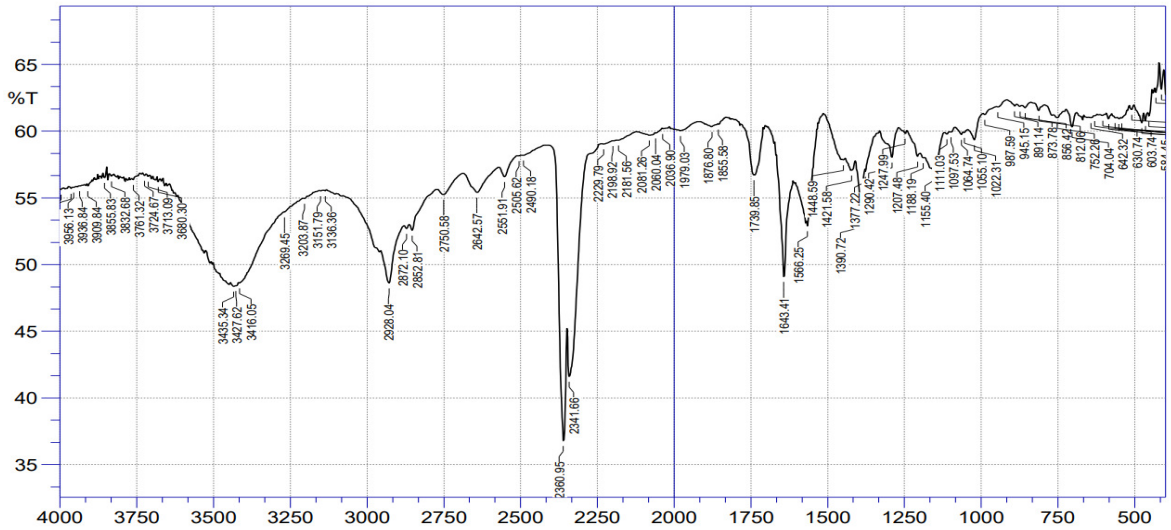



**Fig 14: FTIR spectrum of PEG 600**

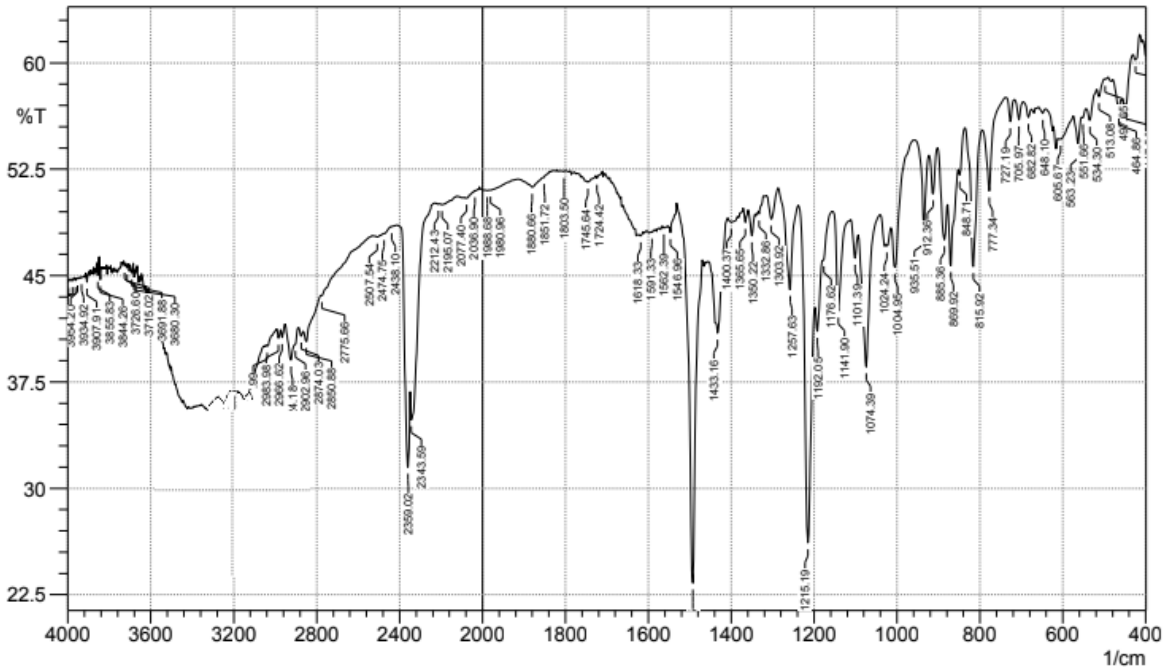



**Fig 15: FTIR spectrum of optimised formulation of nebivolol SNEDDS (F14)**

## 2. *Globule size and zeta potential*

The mean globule size of F14 was 165.2 nm indicating nanoparticle range that facilitates absorption. The zeta potential (mean) values of SNEDDS formulations were found to be in between -13.2 mV. The zeta potential value > 5 mV provide an excellent stability. [23] (Figures 16 and 17)

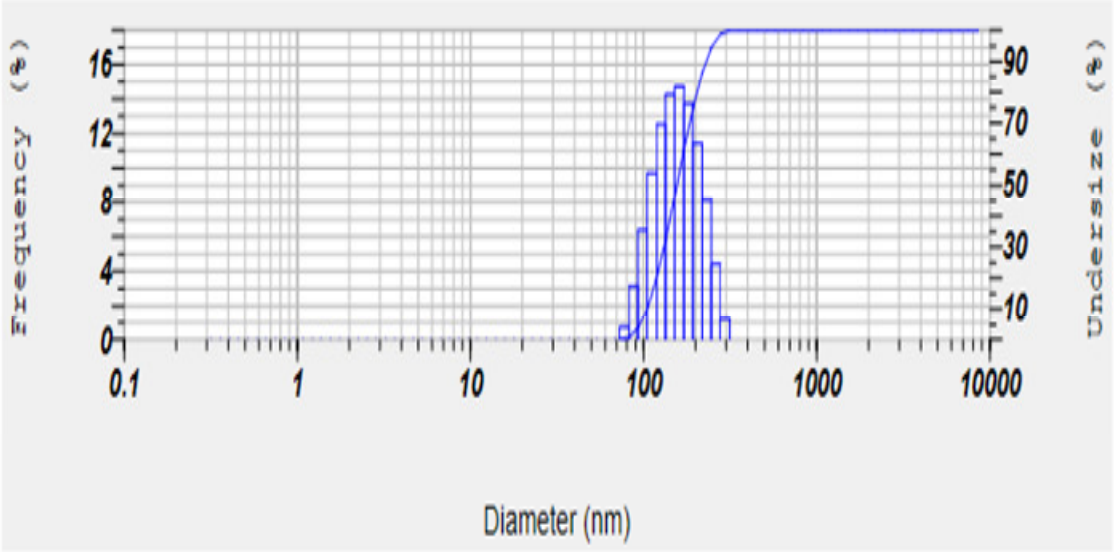



**Fig 16: Particle size of optimised SNEDDS formulation of nebivolol (F14)**

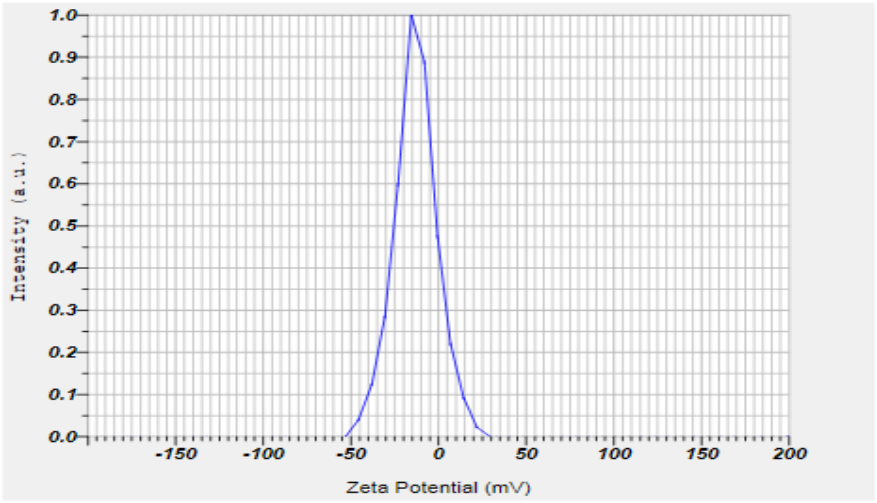
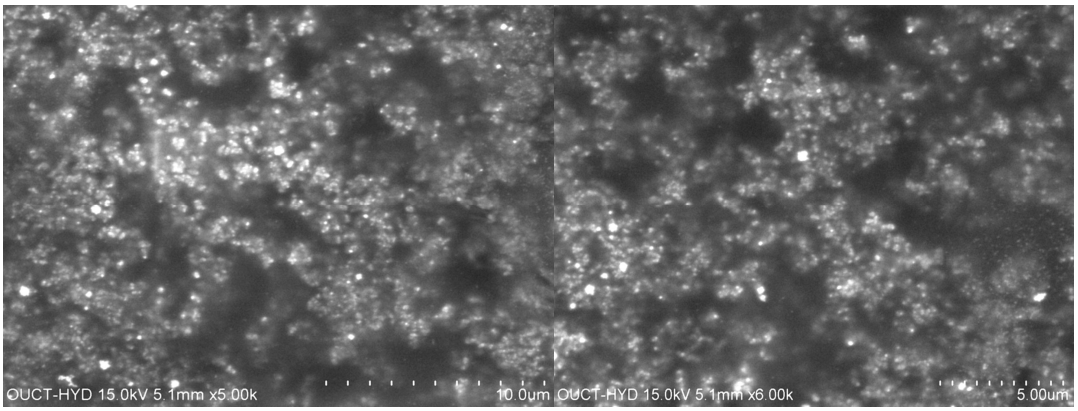



**Fig 17: Zeta potential of optimised SNEDDS formulation of nebivolol (F14)**

### *3. SEM studies*

Figure 18A and 18B show scanning electron microscopic images of the nebivolol-optimized SNEDDS formulation F14. The formulation appeared to be spherical and smooth-surfaced, and globule size analysis confirmed these findings, with all droplets being less than 100 nanometres.




**18(A)** **18(B)**

**Fig 18: SEM images of optimised formulation of nebivolol SNEDDS F14 (A and B)**

### *O. Forced Degradation and Accelerated Stability Studies of Optimized SNEDDS*

Forced degradation and accelerated stability studies were conducted in order to know the stability of nebivolol in the gastric environment and in SNEDDS formulation. The degradation of nebivolol from optimised nebivolol SNEDDS formulation was significantly less when compared to the pure drug degradation. (Table 4)

**TABLE 4:** Percent Degradation of nebivolol from Pure Drug and Optimized nebivolol SNEDDS in Forced Degradation Study

| **Formulation code** | **Time (hr) / Diluting Solvent** | **% Drug Degraded (%, mean ± SD, n=3)** | | | | |
|---|---|---|---|---|---|---|
| | | **0 Hour** | **4th Hour** | **6th Hour** | **12th Hour** | **24th Hour** |
| Pure drug | Methanol | 0.02 ± 1.55 | 0.011 ± 0.24 | 0.01 ± 1.92 | 0.010 ± 1.27 | 0.10 ± 0.65 |
| | Water | 0.01 ± 1.25 | 0.01 ± 1.42 | 0.02 ± 1.65 | 0.04 ± 0.84 | 0.05 ± 1.59 |
| | 0.1 N HCl | 0.07 ± 1.35 | 26.85 ± 1.22 | 28.33 ± 1.06 | 43.74 ± 1.35 | 62.31 ± 1.92 |
| | pH 6.8 phosphate Buffer | 0.01 ± 0.27 | 0.02 ± 1.12 | 0.12 ± 1.44 | 0.08± 1.07 | 0.07 ± 1.96 |
| F14 | Methanol | 0.01 ± 1.85 | 0.12± 0.59 | 0.17 ± 0.62 | 0.02 ± 1.01 | 0.01 ± 1.01 |
| | Water | 0.02 ± 1.19 | 0.28 ± 0.84 | 0.01 ± 1.85 | 0.12 ± 1.43 | 0.07 ± 1.22 |
| | 0.1 N HCl | 0.01 ± 1.75 | 0.05 ± 1.12 | 12.47 ± 1.07 | 28.12 ± 1.26 | 33.85 ± 2.07 |
| | pH 6.8 phosphate Buffer | 0.02 ± 1.22 | 0.05 ± 0.41 | 0.07 ± 1.74 | 0.04 ± 0.65 | 0.10 ± 1.35 |

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

***P. 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 F14** | **% Drug content** | **% Entrapment efficiency** | ***In-vitro* drug release (%)** |
|---|---|---|---|
| 0 days | 99.23±0.14 | 98.51±1.02 | 99.96±0.59 |
| 30 days | 99.12±0.36 | 98.38±0.81 | 99.72±1.07 |
| 60 days | 98.97±0.19 | 98.27±0.46 | 99.58±0.68 |
| 90 days | 98.81±0.27 | 98.13±0.86 | 99.35±1.92 |

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

## IV. CONCLUSION

In our research, the potency of a self-nanoemulsifying drug delivery system was successfully investigated in order to provide an effective system for delivery of nebivolol. Based on the results of the solubility tests in various excipients, we selected the optimal oil, cosolvent, surfactant, and cosurfactant. Through the construction of a ternary phase diagram, the optimal formulation of nebivolol SNEDDS containing nebivolol was found to be Corn oil – caproic acid-PEG600.The particle size, zeta-potential and in vitro dissolution of the resultant emulsion after self-emulsification were determined. The average droplet size of the optimal formulation was 165.2 nm, and the average zeta-potential was -13.2 mV. SNEDDS- has a smaller particle size enhanced drug release of about 99.96% in 60 min which is about 3-fold higher than that of pure drug (32%). Based on forced degradation and stability studies, the SNEDDS can be considered as suitable formulation approach for improving the therapeutic efficiency of nebivolol.

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