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DEVELOPMENT OF SELF EMULSIFYING DRUG DELIVERY SYSTEM OF NEBIVOLOL FOR THE IMPROVEMENT OF SOLUBILITY AND DISSOLUTION

B. Srinivasa Rao, Ch. Ramanamma and K. A. Chowdary*

Department of Pharmaceutical Technology St. Ann's College of Pharmacy, Cantonment, Viziangaram, Pin: 535003, Andhra Pradesh, India.

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***Corresponding Author**
Dr. K. A. Chowdary
Department of Pharmaceutical Technology St. Ann's College of Pharmacy, Cantonment, Viziangaram, Pin: 535003, Andhra Pradesh, India.

ABSTRACT

Nebivolol is a β_1-Receptor blocker, used in the treatment of hypertension belongs to BCS class II with poor water solubility. In the present work an attempt has been made to improve the solubility, dissolution by self-emulsifying drug delivery system. Solubility studies are performed by using various oils, surfactants and co surfactants with nebivolol. Micro emulsion region was formed by preparing ternary phase diagram in ratio at 0.15: 0.85 was selected as the self-emulsification region for the development of optimized formulation. Drug excipient interaction studies were performed by using FT-IR. Time of emulsification, freezing and thawing, in vitro dissolution parameters were evaluated. Self-emulsifying drug delivery system of nebivolol was prepared by using oleic acid (oil), Tween 20 Surfactant) and polyethylene glycol 400 (Co surfactant) and vortex the mixture at 40°C and packed in hard gelatine capsule size of '00'. In vitro dissolution was carried out by USP II using 6.8 pH buffer at 75 RPM and absorbance was measured at 281nm using UV Visible spectroscopy. From the studies, the optimized SEDDS was containing 15% of oleic acid, 50% of Tween 20 & 35% of polyethylene glycol 400. The optimized formulation NF5 was showing improve in drug release within 60 minutes and followed by first order drug release mechanism.

KEYWORDS: Nebivolol, SEDDS, Oleicacid, Polyethylene glycol 400.

INTRODUCTION

The oral route is generally preferred route for chronic drug therapy. Numerous potent lipophilic drugs exhibit low oral bioavailability due to their poor aqueous solubility

properties. For this class of compound defined as "low solubility/ high permeability class II, dissolution in the environmental lumen is the rate controlling step in the absorption process. Efforts are ongoing to enhance oral bioavailability of lipophilic drug in order to increase their clinical efficacy.[1] Several approaches have been developed to enhance the release rate by increasing the solubility.[2,3] One such approach is the use of self-emulsifying drug delivery systems (SEDDS). Emulsions are used as vehicles for the administration of drugs, especially due to its potential of enhancing the oral bioavailability of poorly absorbed drugs.[4] Self-emulsifying drug delivery systems (SEDDS) are class of emulsion that have received particular attention as a means of enhancing oral bioavailability of poorly absorbed drugs. These systems are essentially mixes of oil and surfactant (sometimes with added co-surfactant) that form emulsion on mixing with water with little or no energy input.[5] Nebivolol is used to treat high blood pressure. Lowering high blood pressure helps prevent strokes, heart attacks and kidney problems. This medication belongs to a class of drugs known as beta blockers. It works by blocking the action of certain natural substances in body, such as epinephrine, on the heart and blood vessels. This effect lowers heart rate, blood pressure and strain on the heart. However, the low aqueous solubility and poor dissolution of this molecule in gastric fluid affects its rate of absorption, resulting in a low and variable oral bioavailability.

The pharmacokinetic features of nebivolol vary according to the phenotype of the metabolizer. After a 15-mg dose, peak plasma concentrations were reached at 0.5 to 2 hours in extensive metabolizers and in 3 to 6 hours in poor metabolizers. Absorption of nebivolol is very similar to that of an oral solution. The presence or absence of food does not alter the drug's kinetic profile; therefore, nebivolol may be taken without regard to meals. Nebivolol is highly protein-bound, mostly to albumin at 98%, independent of its concentrations. The half-life of nebivolol varies as well: 10.3 hours in extensive metabolizers and 31.9 hours in poor metabolizers.

Nebivolol undergoes extensive first-pass metabolism through the cytochrome P450 2D6 enzyme system. Exhibits an oral bioavailability of about 12% for extensive metabolizers and 96% for poor metabolizers and is characterized by poor absorption from the G.I. tract following oral administration.[6] The objective of the present research work was to perform solubility studies in various oils and surfactants along with the co solvents and to develop an optimum SEDDS for nebivolol. Present investigation was aimed to increase oral

bioavailability of nebivolol. Self-emulsifying drug delivery system was developed to enhance oral solubility and in-vitro dissolution of drug. SEDDS are physically stable formulations that are easy to manufacture. Thus, for lipophilic drugs these systems may offer an improvement in the rate and extent of absorption and results in more reproducible plasma level concentrations.

MATERIALS AND METHODS

Materials

Nebivolol was purchased from Yarrow Chem Products Ltd, Mumbai. Polyethylene glycol 400 was obtained from Ozone Intenational, Mumbai, Ahmedabad. Tween 20 was obtained from Loba Chemie Pvt Ltd, Mumbai. Oleic acid was received from Burgoyne Burbidges Ltd, Mumbai.

Solubility studies

Excess amount of nebivolol was added to 2 mL of each excipients were placed in test tubes and the mixture was vortexed and heated in a water bath to facilitate drug solubilization. Mixing of the systems was performed using a vortex mixer. The mixture was finally kept at ambient room temperature (25°C) under continuous shaking for 24 hours to attain equilibrium. After reaching equilibrium, each vial was centrifuged at 3000 rpm for 5 min and excess insoluble nebivolol was discarded by filtration using a membrane filter (0.45 µm, 13 mm, Whatman, India). The concentration of nebivolol was then quantified by UV spectrophotometer. Solubility study was performed at three times and standard deviation was calculated.[7,8,9,10,11] Solubility of nebivolol in different systems was shown in the following Table 1.

Table 1: Solubility of nebivolol in various vehicles at 25°C (Mean± SD; n=3)

S. No.	Vehicles	Solubility (mg/mL)
1	Olive oil	0.57±0.24
2	Sesame oil	0.344±0.37
3	Oleic acid	2.124±0.98
4	Tween 20	46.35±1.04
5	Tween 40	21.2±0.46
6	Tween 80	3.98±0.91
7	PEG 400	18.5±0.012
8	Propylene Glycol	12.8±0.87
9	Ethanol	0.34±0.054
10	Water	0.24±0.033

Construction of ternary phase diagram

Self-emulsifying performance of self-emulsion (SE) mixture was assessed from their ternary phase diagrams. Only the specific combinations of oil, surfactant and a co surfactant in the specific composition range were observed to produce a fine micro emulsion upon aqueous dilution. To check emulsification efficiency of SE mixtures, test for emulsification was performed on all combinations and the resultant dispersions were visually assessed. The dispersions either formed a clear micro emulsion, a slightly turbid emulsion or a milky emulsion which immediately was phase separated. A series of formulations were prepared with the drug using varying concentrations of oil, surfactant and co-solvent in the glass test tube and mixed by vortexing until a clear solution was obtained. The mixture was stored at room temperature until used.

Fourier transform-infrared spectroscopy

FT-IR spectroscopy was performed using FT-IR model Shimadzu 8400, Japan attached to an attenuated total reflectance (ATR) accessory. ATR was fitted with a single bounce diamond at 45˚ internally reflected incident light providing a sampling area of 1 mm in diameter with a sampling depth of several microns. Nebivolol and mixture of ingredient was analyzed. A small amount of the sample was directly placed on the diamond disk and liquid sample kept in liquid sample holder. Sample was scanned for absorbance over the range from 4000 to 400 wave numbers (cm^{-1}) at a resolution of 1 cm^{-1}.

Self-emulsification time

The self-emulsification time is determined by using USP dissolution apparatus II at 50 rpm, where 0.5 g of SEDDs formulations is introduced into 250 mL of 0.1N HCI or 0.5% SLS solution. The time for emulsification at room temperature is indicated as self-emulsification time for the formulation.[13]

Drug content

All the batches were assayed spectrophotometrically for the drug content at the wavelength 281 nm with proper dilution of formulations taking phosphate buffer (PH 6.8) as blank.[14,15]

***In vitro*dissolution study**

Dissolution study of SEDDS formulations were determined using rotating paddle dissolution apparatus (USP type II Lab India DS 8000) used at 37°C ± 0.5°C and a rotating speed of 75 rpm in 900 mL of phosphate buffer (pH 6.8). The SEDDS formulation was placed in a hard

gelatine capsule held to the bottom of the vessel using copper sinkers. During the release studies, samples were withdrawn and subjected to UVSpectrophotometric analysis. The sample volume was replaced each time with equal quantity of fresh medium.[16]

Robustness to dilution

These systems when diluted with excess of water, standard phosphate buffer (pH 6.8) and 0.1N HCl (500-900 mL) and were stored for 12 hours give no precipitation or phase separation and are thus said robust to dilution.[17]

Freeze thaw cycle

Three freeze thaw cycles between -4°C and +40°C with storage at each temperature for not less than 48 hours was done for the formulations.[18]

Drug-excipients compatibility study

This was carried out by FT-IR analysis of pure drug, oils and surfactants (Polyethylene glycol 400, Oleic acid and Tween20) and their formulations to study the possible interaction between drug and polymers.[19]

RESULTS AND DISCUSSIONS

Visual observations and construction of ternary phase diagram

From the above chosen oils, surfactant and co-solvents were taken in different ratios (Table 2) for the construction of ternary phase diagrams to know the emulsion and micro-emulsion domains such that at particular concentration of oil, surfactant and co-solvent ratios, a stable self-emulsifying formulation is formed. The Self emulsification process is affected on the concentration of Tween 20 and Polyethylene glycol 400 and their ratio. Micro emulsion region was appeared at surfactant concentration (10-75%) of w/w, co-solvent concentration at (10- 65%). So the concentration of oil, surfactant and co-solvent was selected in these domains for the study. On the basis of ternary phase diagrams readings, it was observed that region of emulsification in case of Tween 20, PEG 400 ratio at 0.5:0.5 is 20-25% and 25-30% in case of Tween 20, PEG 400 at 0.15:0.85 is 20-75% and 10-65%, in case of Tween 20, PEG 400 at 0.1:0.9 is 30- 75% and 15-60%, it was therefore, decided to use Tween 20 and PEG 400 ratio 0.15: 0.85 and 0.5:0.5 for further development of self-emulsifying drug delivery system of nebivolol.[12]

Table 2: Composition of combinations containing oleic acid, Tween 20 and polyethylene glycol 400 (oil, surfactant, co-solvent

Formulation Code	Oil (%)	Surfactant (%)	Co Solvent (%)	Visual observation	Inference
ANT1(0.5:0.5)	50	25	25	Transparent	Stable
ANT2	50	20	30	Transparent	Stable
ANT3	50	30	20	Turbid	Unstable
ANT4	50	40	10	Turbid	Unstable
ANT5	50	10	40	Turbid	Unstable
BNT1(0.3:0.5)	30	35	35	Turbid	Unstable
BNT2	30	20	50	Turbid	Unstable
BNT3	30	50	20	Turbid	Unstable
BNT4	30	15	55	Turbid	Unstable
BNT5	30	55	15	Turbid	Unstable
CNT1(0.15:0.85)	15	20	65	Transparent	Stable
CNT2	15	65	20	Transparent	Stable
CNT3	15	75	10	Transparent	Stable
CNT4	15	10	75	Turbid	Un Stable
CNT5	15	70	15	Turbid	Unstable
DNT1(0.1:0.9)	10	45	45	Turbid	Unstable
DNT2	10	60	30	Turbid	Unstable
DNT3	10	30	60	Transparent	Stable
DNT4	10	75	15	Transparent	Stable
DNT5	10	15	75	Turbid	Unstable

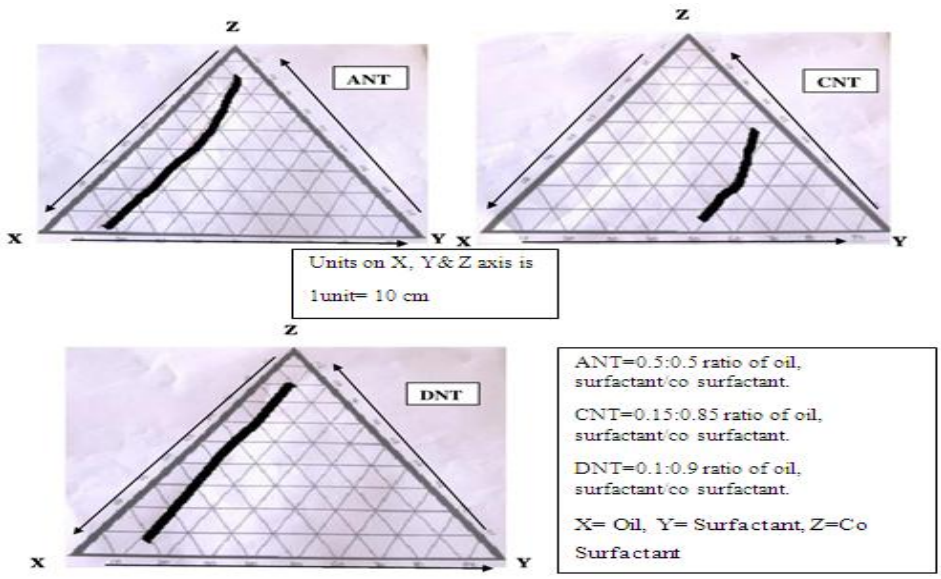

Fig.1: Ternary phase diagram of nebivolol in different ratios

Solubility studies

Solubility studies were performed to identify suitable oily phase, surfactants, and co surfactants for the development of SEDDS of nebivolol. An important consideration when

formulating a self-emulsifying formulation is to avoid precipitation of the drug on dilution in the gut lumen *invivo*. The components used in the system should have high solubilization capacity for the drug, ensuring the solubilization of the drug in the resultant dispersion.[17]

The results of solubility studies are reported in Table 1 and Figure 2. It is evident from the results that, among oils, sesame oil (0.912 ± 0.008 mg/mL) exhibited the highest solubilization capacity for the drug nebivolol, and among surfactants, Tween 20 (0.905 ± 0.035 mg/mL) showed the highest solubility followed by PEG 400 (0.747 ± 0.041 mg/mL) among co surfactants. Hence, for the preparation of SEDDS, sesame oil, Tween 20, and PEG 400 were chosen as an oil, surfactant, and co surfactant.

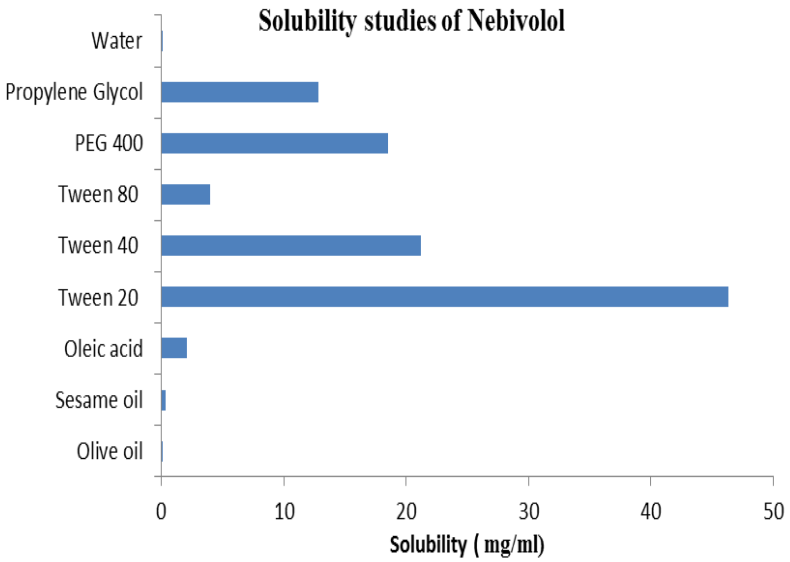

Fig.2: Solubility studies of nebivolol in various systems

Preparation of SEDDS of nebivolol

The liquid SEDDS formulations were prepared by standard ad mixture method. Required quantity of drug was dissolved in the oleic acid. Tween 20 (surfactant) and PEG 400 (co surfactant) were mixed separately and then surfactant/co surfactant mixture was added to oil drug mixture, while stirring at high speed using magnetic stirrer at optimum temperature. On the basis of region of emulsification in pseudo ternary phase diagram, Oleic acid, Tween 20, PEG 400 were taken in different concentrations to prepare the formulations. Based on the composition of the surfactant, co solvent and oil, different formulations were prepared for 2mL as shown in Table 3 and finally required quantities of SEDDS formulations was dispensed in '00' size hard gelatine capsule.

Table 3: Formulation of nebivolol Self emulsifying drug delivery in various systems of compositions

Formulation Code	Drug (mg)	Oil (%)	Surfactant (%)	Co solvent (%)
NF1	80mg	50	10	40
NF2	80mg	50	35	15
NF3	80mg	15	20	65
NF4	80mg	15	35	50
NF5	80mg	15	50	35
NF6	80mg	15	65	20
NF7	80mg	15	70	15

Content uniformity

The formulations which contain 50 mg of nebivolol equivalent weights were tested for amount of drug present in each capsule. The contents present inside the capsules were emptied into 100mL volumetric flask. 20 mL methanol was added and mixed it for 20 min to dissolve the drug. The volume was made to 100 mLwith methanol. The dispersion was filtered using Whatmann filter paper. Dilutions are made in 6.8 phosphate buffer and absorbance of sample solution was determined at 281nm .So that the drug present in the single capsule can be known. Results of content uniformity were shown in Table 4. It showed all the batches have a minimum of 98% content uniformity. Among all the batches NF2 had highest content uniformity 99.12%.

Table 4: Drug content of SEDDS formulations (mean±S.D, n=3)

Formulation Code	Drug Content (%)
NF1	101.17±1.09
NF2	100.98±0.98
NF3	96.08±0.76
NF4	96.8±0.65
NF5	98.34±0.54
NF6	98.86±0.75
NF7	99.36±0.087

Determination of time of emulsification

Emulsification times of the prepared formulations are shown in Figure 3, it was observed that emulsification time varied from 1.01 minutes to 6.6 minutes[19] were shown in Table 5. It was less in case where co surfactant concentration was low and maximum emulsification time was observed in case where all three components were at their higher levels. Emulsification time was minimum in NF7 (1.01 min) and maximum with formulation NF1 (6.6 min).

Table 5: Emulsification time of different SEDDS formulations (mean±S.D, n=3)

Formulation Code	Self-emulsification time (sec)
NF1	396
NF2	310
NF3	210
NF4	120
NF5	98
NF6	65
NF7	61

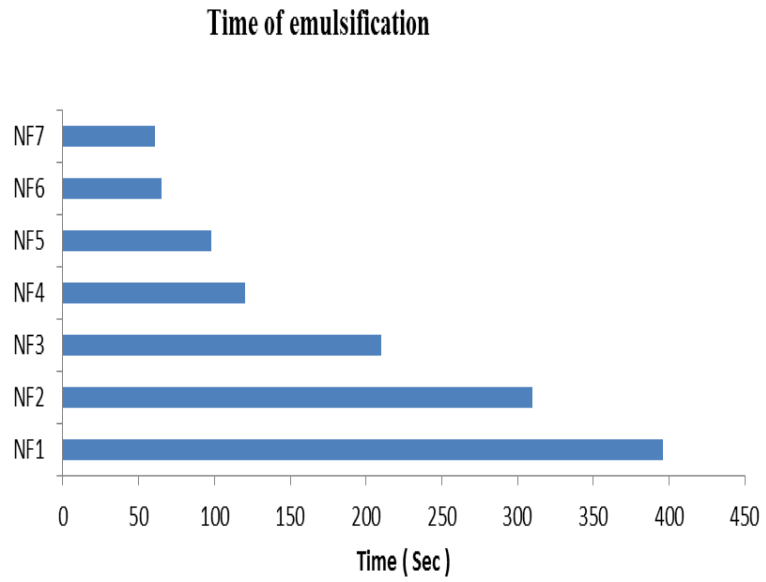

Fig 3: Emulsification time for various formulations

Robustness to dilution

Robustness to dilution was performed diluted with excess of water, standard phosphate buffer pH 6.8 and 0.1N HCl (500-900 ml) and was stored for 12 hours gives no precipitation or phase. The optimized oil and SEDDS mix concentrations are robust to all dilutions with various dissolution media. Robustness to dilution, with excess of water, 0.1M HCl and pH 6.8 phosphate buffers, show no precipitation or phase separation and were shown in Table 6 no significant effect of pH on the optimized formulations NF2 to NF7 was observed. It confirms the preparations were robust to high dilution and variations in pH.

Table 6: Robustness to dilution of various SEDDS formulations (mean±S.D, n=3)

Formulation Code	Distilled Water	0.1 N HCl	6.8 pH buffer
NF1	No Precipitation	Precipitation	No Precipitation
NF2	No Precipitation	No Precipitation	No Precipitation
NF3	No Precipitation	No Precipitation	No Precipitation
NF4	No Precipitation	No Precipitation	No Precipitation

NF5	No Precipitation	No Precipitation	No Precipitation
NF6	No Precipitation	No Precipitation	No Precipitation
NF7	No Precipitation	No Precipitation	No Precipitation

Freezing and thawing

From the seven formulations shown in above table without NF1 and NF3 remaining all are neither phase separation nor precipitation of drug in micro emulsions after 24 hr. It representing that these formulations are resulting in stable micro emulsion upon dilution. Hence the formulations which were stable for precipitation after study were selected for further investigation and were shown in Table 7.

Table 7: Freezing and thawing of SEDDS formulations (mean±S.D, n=3)

Formulation code	Centrifugation	Freezing and Thawing method	
		-°4 C for 2 days	°40 C for 2 days
NF1	Phase Separation	Phase Separation	Phase Separation
NF2	No Phase Separation	No Phase Separation	No Phase Separation
NF3	Phase Separation	Phase Separation	Phase Separation
NF4	No Phase Separation	No Phase Separation	No Phase Separation
NF5	No Phase Separation	No Phase Separation	No Phase Separation
NF6	No Phase Separation	No Phase Separation	No Phase Separation
NF7	No Phase Separation	No Phase Separation	No Phase Separation

Dissolution study

The quantitative *invitro* release test was performed in 900 mL of buffer pH 6.8 using US Pharmacopeia XXIV dissolution apparatus II. The paddles were rotated at 75 rpm. The SEDDS formulations were put into hard gelatin capsules (00 size) and used for drug release studies; results were compared with those of plain nebivolol. During the release studies, a 5mL sample of medium was taken out and subjected to drug analysis using UV Visible spectrometer at 281 nm. The removed volume was replaced each time with 5 mL of fresh medium at different interval 0, 5, 10, 20, 30, 40, 50 and 60 min.

RESULTS

In vitro dissolution studies were performed for NF2, NF4, NF5, NF6, NF7 and pure drug were conducted. The results of in vitro drug release studies from the pure drug and SEDDS of all formulations of nebivolol described in the below Table 8. The percent drug release of SEDDS of nebivolol and pure drug was plotted against time. A comparison of in vitro drug release profile of pure drug & SEDDS formulations are given in the below Figure 4**.** Based on the drug release comparison studies, it was observed that maximum drug release from the

SEDDS from all formulations is higher when compared with that of the pure drug. The order of drug release in decreased order NF5 > NF4 > NF7 > NF6 > NF2. NF5 and NF4 shows maximum release and have more than 90% release within 50 min. From all the formulations, NF5 was selected for the optimum formulation due to the maximum release with less self-emulsification time. Drug release kinetics was calculated for all formulations. From the regression value of all formulations, all formulations follow first order release mechanism.

Table 8: In vitro dissolution profiles of various formulations and pure drug (mean±S.D, n=3)

Time (min)	NF2	NF4	NF5	NF6	NF7	Pure drug
0	0	0	0	0	0	0
5	7.12±0.31	8.57±0.75	6.57±0.88	6.18±0.84	6.57±0.85	11.4±0.88
10	33.17±0.16	33.14±0.64	41.86±0.77	39.8±0.75	41.54±0.88	39.5±0.97
20	43.18±0.81	45.21±0.87	55.64±0.78	47.32±0.87	56.32±0.89	49.32±0.87
30	59.75±0.86	67.35±0.65	63.8±0.75	59.32±0.73	65.98±0.99	51.97±0.94
40	67.21±0.75	78.32±0.87	76.1±0.82	67.96±0.76	71.06±0.77	54.84±0.83
50	71.21±0.51	89.35±0.86	95.75±0.71	86.95±0.62	78.24±0.65	55.83±0.76
60	77.13±0.51	95.21±0.85	98.43±0.42	91.5±0.63	92.3±0.65	54.23±0.89

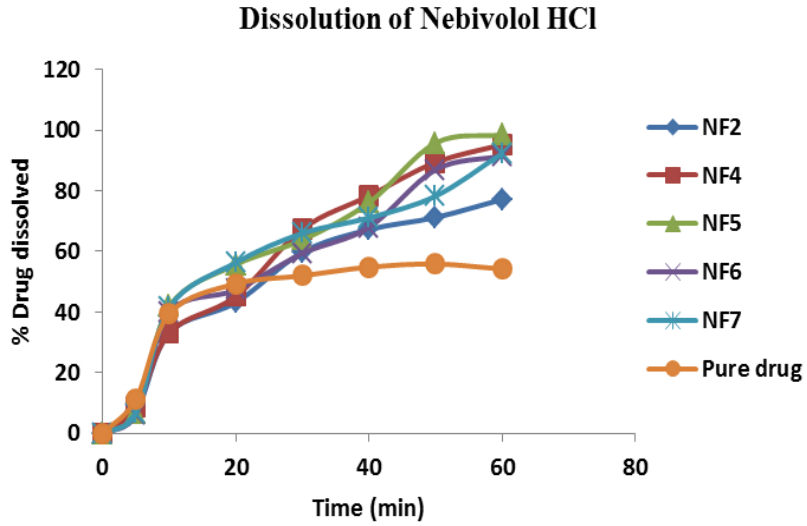

Fig.4: Dissolution profiles of SEDDS formulations and pure drug

Comparison of optimized formulation and pure drug

Drug release behaviour of optimized formulation, marketed tablet and pure drug was studied in 0.1 N hydrochloric acid and compared and the comparison of their dissolution profiles is shown in Figure 5. The dissolution profiles of pure, marketed and optimized batch shows that pure drug released very slowly (32.26%) and marketed tablet released 70.23% whereas

optimized formulation released 89.95% in 3 hrs. These results indicated that release of nebivolol was significantly enhanced by SEDDS.Drug dispersed perfectly in SEDDS and could be released faster due to small droplet size which permits a faster dissolution of drug into aqueous phase.

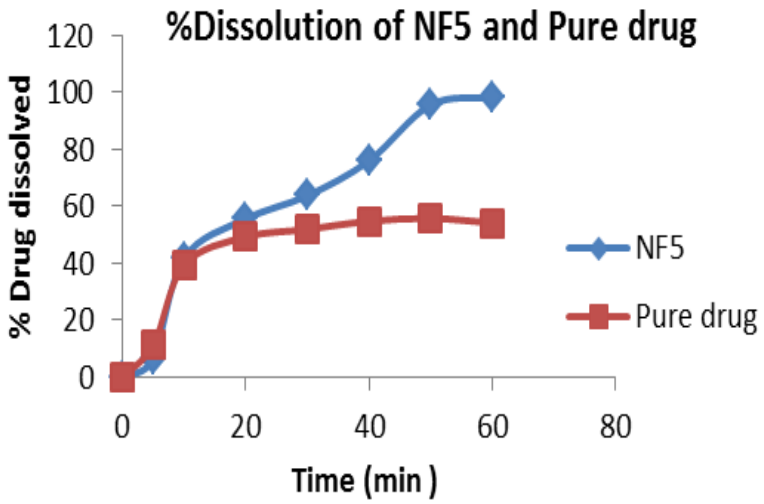

Fig.5: Dissolution profiles of optimized SEDDS formulation (NF5) and pure drug

III. K. RELEASE KINETICS OF OPTIMIZED BATCH

Many models have been proposed to explain the drug dissolution profiles where drug release is a function of time (t) related to the amount of drug dissolved from pharmaceutical dosage form. (Here self-emulsifying drug delivery system) The drug release kinetics followed maximum is first order for all formulations suggesting drug release from spherical surface (Figure 6).

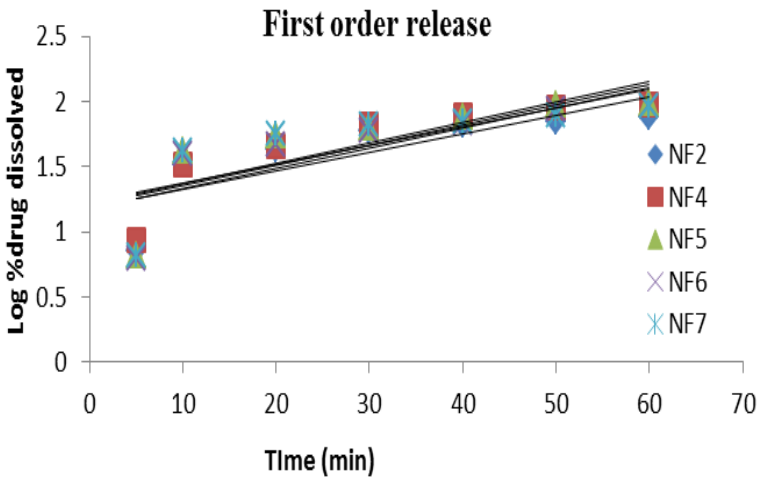

Fig.6: First order rate release profiles of SEDDS formulations

Table 9: Drug release kinetics of SEDDS showing ´r` value

Formulation Code	First order	Zero order
NF2	0.976	0.876
NF4	0.970	0.921
NF5	0.917	0.899
NF6	0.950	0.920
NF7	0.931	0.874

FTIRstudies of optimized SEDDSformulations

An FT-IR spectrophotometer equipped with attenuated total reflectance accessory was used to obtain the infrared spectra of drug in the isotropic mixtures of excipients. Analysis of pure drug, oleic acid, Polyethylene glycol 400, Tween 20, physical admixtures of the drug with the excipients (in 1:2 ratio) were carried out using FT-IR with KBr disc. All the samples were dried under vacuum prior to obtaining any spectra in order to remove the influence of residual moisture. For each of the spectrum were obtained at a resolution of 4 cm^{-1} from a frequency range of 4000–600cm^{-1} as shown in Figure 7 and 8. The stretching's were illustrated in the Table 10.

From the results of the spectra, it was found that there was no interaction between the drug and excipients used in the SEDDS of Nebivolol.

Table 10: Drug excipient interaction studies using FT-IR (Fourier Transform Infrared Spectroscopy)

Nebivolol interpretation showing peaks at different functional groups	optimized SEDDS interpretation showing peaks at different functional groups
NH-3826.36	3799.48
OH-3741.48	3749.42
CH STRECH-1427.97	1458.87
C-O-C-1139.20	1156.43
F-1094.22	1100.64

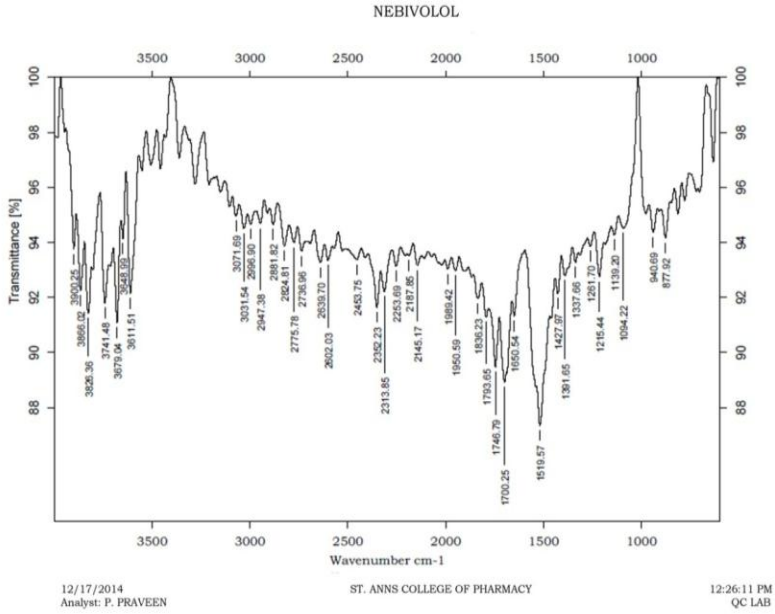

Fig. 7: FTIR of pure API

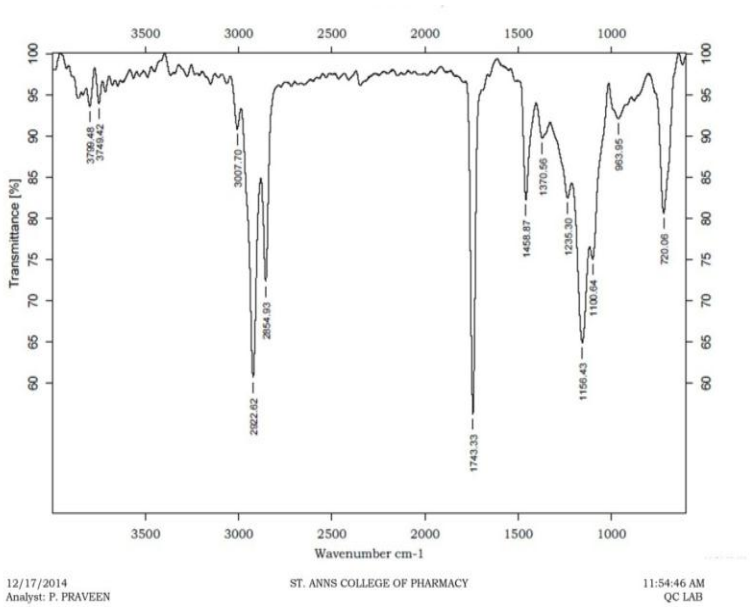

Fig. 8: FTIR of pure API and Excipients

CONCLUSION

A SEDDS formulation of poorly water soluble drug nebivolol was formulated as liquid for directly filling in hard gelatine capsule '00' size for oral administration. SEDDS of nebivolol was optimized by using solubility studies, self-emulsification time, robustness to dilution, drug content, freezing and thawing and in vitro drug release. The optimized nebivolol SEDDS composed of 15% oleic acid, 50% Tween 20 and 35% polyethylene glycol 400 with self-emulsification time 98 seconds, Drug content 98.34±0.54 and within vitro drug release

up to 98.43±0.42 within 60 minutes as compared with pure drug. The results from the study show the utility of SEDDS to enhance the solubility and dissolution of poorly soluble compound like nebivolol.

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