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Preparation and Evaluation of Solid Dispersion of Nebivolol Using Solvent Evaporation Method

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ABSTRACT

Nebivolol is a pharmaceutical drug used for the treatment of Hypertension. It is characterized with poor solubility which limits its absorption and dissolution rate which delays onset of action. In the present study, fifteen formulations of solid dispersions were prepared with 1:1:1, 1:5:2 and 1:3:1.5 ratios of drug: carrier: surfactant by solvent evaporation method. There was significant improvement in the rate of drug release from all 15 solid dispersions and the formulation (SD14) comprising Nebivolol: Kleptose HPB: SLS in 1:5:2 ratio has shown enhanced solubility about 42 folds and significant improvement in the rate of drug release i.e. From powder X-ray diffraction (p-XRD) and by scanning electron microscopy (SEM) studies it was evident that polymorphic form of Nebivolol has been converted into an amorphous form from crystalline within the solid dispersion formulation. The present study demonstrated that formulation of Nebivolol solid dispersion is a highly effective strategy for enhancing the bioavailability of poorly water soluble drug Nebivolol.

Keywords: Nebivolol, Solid dispersions, Hypertension, Kleptose HPB.

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INTRODUCTION

An oral route of drug administration is the most preferred route of drug delivery due to convenience and ease of ingestion. A solid dosage form is a comfortable and familiar means of taking medication. Hence, a patient compliance and drug treatment are usually more effective with orally administered medications than other routes of administration. [1] At least 40% of the new chemical molecules tested are

drugs having poor aqueous solubility. Many methods are available to improve dissolution rate, solubility characteristics, including salt formation, micronization, and addition of solvent or surface-active agents. Solid dispersion is one of these methods, which was most widely and successfully applied to improve the solubility, dissolution rates and consequently the bioavailability of poorly soluble drugs. [2] Solid dispersion technology is one of the most promising and

extensively performed approach to improve the dissolution rate of insoluble compounds. Ease of scalability, its conversion to solid dosage forms such as capsules, tablets, taste masking strips and implants are some of the advantages offered by solid dispersion over other approaches. [3]

Nebivolol hydrochloride is chemically known as α , α -[iminobis (methylene)] bis [6-fluoro-3,4-dihydro-2H-1-benzopyran-2-methanol]hydrochloride. It is a highly selective β 1-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 preparing solid dispersions with various polymers such as Soluplus, Kolliphor P188, Kolliphor ELP, Labrafac CC and Kleptose HPB. The prepared solid dispersions were evaluated for solubility study, drug content and *in vitro* dissolution rate studies.

MATERIALS AND METHODS

Materials

Nebivolol pure drug was generous gift from Aurobindo Pharma Ltd, Hyderabad, India. Kleptose HPB and PEG 6000 were obtained from BASF, Mumbai. Kolliphor P188, Labrafac CC, Kolliphor ELP were obtained from Signet Chemical Corp. Pvt. Ltd, Mumbai. Soluplus were gifted from BASF, Germany. PEG 400, Span 40, Tween 80, and PVP K-25 and were gifted from Dow Chemicals, USA. All other chemicals used were of analytical grade.

Preliminary solubility studies of Nebivolol

Solubility measurements of Nebivolol were performed according to a published method (Higuchi and Connors, 1965). An excess amount of Nebivolol was added to 25 ml of aqueous solution of water soluble carriers like PEG 6000, Labrafac CC, Kolliphor ELP, Soluplus, Kleptose HPB, Kolliphor P188, PEG 400, Span 40, Tween 80 and PVPK-25 in screw capped bottles. Samples were shaken for the 24 hours at room temperature. Subsequently, the suspensions were filtered through a Whatman filter paper no 1. Filtered solution was diluted properly with methanol. The diluted solution analyzed for the Nebivolol in UV 280 nm. [5]

Preparation of Nebivolol solid dispersion by the solvent evaporation method

The calculated amount of Nebivolol and the employed polymers of Soluplus, Kolliphor P188, Kolliphor ELP, Labrafac CC, Kleptose HPS and SLS in different drug, polymer and surfactant ratios of 1:1:1, 1:5:2 and 1:3:1.5) (Shown in Table 1) are weighed and mixed together in a porcelain dish. Fifteen different formulae were

prepared by the solvent evaporation method. The mixture was dissolved in the least amount of methanol as a common solvent. Then the solvent was evaporated in oven at temperature 50°C till complete evaporation. The solid dispersions prepared were pulverized in a mortar and sieved. The fraction of the powder that passed through 45 μ m was stored in a desiccator and used for further investigations. [6-7]

Solubility studies of Nebivolol solid dispersion by solvent evaporation method

Solubility measurements of Nebivolol were performed according to a published method. Samples were shaken for the 48 hours at room temperature. Subsequently, the suspensions were filtered through a Whatman filter paper no 1. Filtered solutions were analyzed for the Nebivolol UV 280 nm.

Evaluation of Nebivolol solid dispersions

Solid dispersions obtained from the above method were tested for their % Practical yield, Drug content and *in vitro* release studies.

Percentage Practical Yield

Percentage practical yield was calculated to know about percent yield or efficiency of any method, thus its help in selection of appropriate method of production. SDs were collected and weighed to determine practical yield (PY) from the following equation. [8]

$$\% \text{ Practical Yield} = \frac{\text{Practical Mass (Solid dispersion)}}{\text{Theoretical Mass (Drug + Polymer + Surfactant)}} \times 100$$

Drug content

Solid dispersions equivalent to 10 mg of Nebivolol was weighed accurately and dissolved in 100 ml of methanol. The solution was filtered, diluted suitable and drug content was analysed at λ_{max} 280 nm against blank by UV spectrometer. The actual drug content was calculated using the following equation as follows. [9]

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

In vitro Dissolution study of solid dispersion

The USP dissolution test type II apparatus was used. Amount of samples equivalent to 10 mg of drug were dispersed into the dissolution vessel containing 900 mL of pH 6.8 PBS at 37°C and stirred at 50 rpm. Samples were withdrawn periodically, filtered and replaced with a fresh dissolution medium. After filtration through 0.45 μ m microfilter, concentration of Nebivolol was determined spectrophotometrically at λ_{max} 280 nm. [10]

Characterization

FTIR studies

Instrument used was Shimadzu FTIR-8700 spectrophotometer. In this study, potassium bromide disc method was employed. Pure drug, physical mixtures, and solid dispersion studied by IR. The powdered sample was intimately mixed with dry powdered potassium bromide. The mixture was then compressed into transparent disc under high pressure

using special dies. The disc was placed in IR spectrophotometer using sample holder and spectrum was recorded. [11]

Powder X-ray diffraction (XRD)

X-ray powder diffraction patterns were recorded on an X-ray powder diffraction system (Shimadzu, Japan) using copper target, a voltage of 40 Kv and a current of 30 mA. The scanning was done over 2θ range of 5° to 60° . [12]

SEM (Scanning Electron microscope) studies

The surface morphology of the layered sample was examined by using SEM (Hitachi, Japan). The small amount of powder was manually dispersed onto a carbon tab (double adhesive carbon coated tape) adhered to an aluminum stubs. These sample stubs were coated with a thin layer ($30\text{\AA}$) of gold by employing POLARON-E 3000 sputter coater. The samples were examined by SEM and photographed under various magnifications with direct data capture of the images onto a computer. [13]

Stability studies

Prepared solid dispersions were placed inside sealed 40cc HDPE container with child resistant cap under controlled temperature environment inside stability chamber (Thermo Lab, India) with relative humidity of $75\% \pm 5\%$ RH and temperature of $40^\circ\text{C} \pm 2^\circ\text{C}$ for stability studies. Samples were removed after 1, 2 and 3 months and evaluated for % drug content and *in vitro* dissolution studies.

RESULTS AND DISCUSSION

Preliminary solubility studies of Nebivolol

In case of solid dispersions initially preliminary solubility analysis was carried out to select the appropriate water-soluble carriers for the preparation of solid dispersion in which pure drug solubility was found to be 0.0403 mg/ml (Table 2). From this study, drug and Kleptose HPB in the ratio of 1:1 shown highest drug solubility i.e. $0.886 \pm 0.04 \text{ mg/ml}$, almost 22-fold increase compared to that of pure drug. For all the soluble carriers used in preliminary solubility studies PEG 6000, PVP k 25, PEG 400, Span 40, Tween 80 shown low solubility when compared with other carriers and did not included in the preparation of Nebivolol solid dispersions. The graphical representation of solubility studies of Nebivolol physical mixtures was shown in Figure 1.

Preparation of Nebivolol solid dispersions

Solid dispersions of Nebivolol were prepared by solvent evaporation method using different carriers like Soluplus, Kolliphor P188, Kolliphor ELP, Labrafac CC and Kleptose HPS in three different drug: polymer: surfactant (SLS) ratios of 1:1:1, 1:5:2 and 1:3:1.5 (Table 1). Total 15 formulations were prepared; the mixture was dissolved in the least amount of methanol as a common solvent. Then the solvent was evaporated in oven at temperature 50°C till complete evaporation. The resultant solid dispersion was scraped out with a spatula. Solid dispersions were pulverized in a mortar

and pestle and passed through a $45\mu\text{m}$ sieve before packing in an airtight container, stored in a desiccator and used for further investigations. All the solid dispersions prepared were found to be fine and free flowing powers.

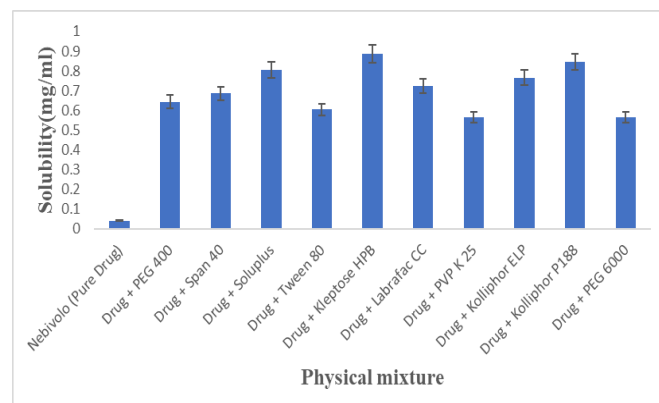


Fig. 1: Preliminary solubility studies of Nebivolol physical mixture



Fig. 2: Preparation of Nebivolol Solid Dispersions

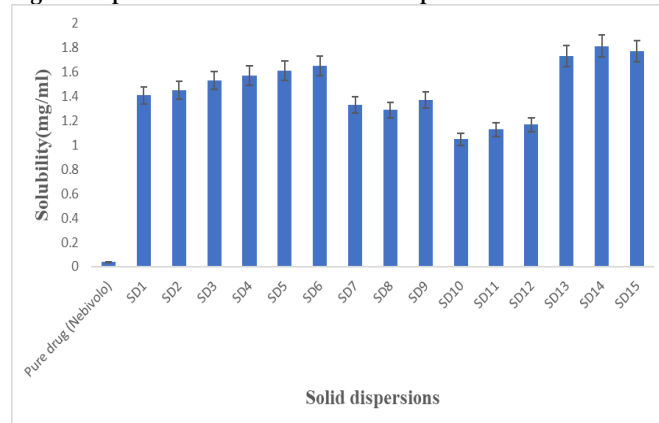


Fig. 3: Solubility studies of Nebivolol solid dispersion

Evaluation parameters

Solubility studies of Nebivolol solid dispersions

Different formulations of Nebivolol solid dispersions were prepared by solvent evaporation method with their respective carriers. After preparation of solid dispersion solubility analysis was carried out. The formulation (SD14) with Drug, Kleptose HPB and SLS in the ratio of 1:5:2 shown highest solubility i.e. $1.8135 \pm 0.07 \text{ mg/ml}$, almost 45-fold compared to that of the pure drug (Pure drug solubility is $0.0403 \pm 0.04 \text{ mg/ml}$). The results are tabulated in Table 3 and graphical representation was shown in Figure 3.

Table 1: Composition of Nebivolol solid dispersions

S. No	Ingredients (Units in mgs)	SD1 (1:1:1)	SD2 (1:5:2)	SD3 (1:3:1.5)	SD4 (1:1:1)	SD5 (1:5:2)	SD6 (1:3:1.5)	SD7 (1:1:1)	SD8 (1:5:2)	SD9 (1:3:1.5)	SD10 (1:1:1)	SD11 (1:5:2)	SD12 (1:3:1.5)	SD13 (1:1:1)	SD14 (1:5:2)	SD15 (1:3:1.5)
1	Nebivolol (mg)	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
2	Soluplus	10	50	30	-	-	-	-	-	-	-	-	-	-	-	-
3	Kolliphor P188	-	-	-	10	50	30	-	-	-	-	-	-	-	-	-
4	Kolliphor ELP	-	-	-	-	-	-	10	50	30	-	-	-	-	-	-
5	Labrafac CC	-	-	-	-	-	-	-	-	-	10	50	30	-	-	-
7	Kleptose HPB	-	-	-	-	-	-	-	-	-	-	-	-	10	50	30
8	SLS	10	20	15	10	20	15	10	20	15	10	20	15	10	20	15
9	Methanol (mL)	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs

Table 2: Preliminary solubility studies of Nebivolol in different polymers

Physical Mixture (1:1)	Solubility(mg/ml) *
Nebivolo (Pure Drug)	0.0403 ± 0.04
Drug + PEG 400	0.644 ± 0.003
Drug + Span 40	0.685 ± 0.13
Drug + Soluplus	0.806 ± 0.01
Drug + Tween 80	0.604 ± 0.04
Drug + Kleptose HPB	0.886 ± 0.05
Drug + Labrafac CC	0.725 ± 0.07
Drug + PVP K 25	0.564 ± 0.11
Drug + Kolliphor ELP	0.765 ± 0.02
Drug + Kolliphor P188	0.846 ± 0.12
Drug + PEG 6000	0.566 ± 0.12

*n= SD ± 3

Table 3: Solubility studies of Nebivolol solid dispersions prepared by solvent evaporation method

S. No.	Formulation code	Solubility (mg/ml) *
1	Pure drug (Nebivolol)	0.0403 ± 0.04
2	SD1	1.010 ± 0.12
3	SD2	1.450 ± 0.17
4	SD3	1.331 ± 0.22
5	SD4	1.171 ± 0.04
6	SD5	1.612 ± 0.01
7	SD6	1.652 ± 0.13
8	SD7	1.129 ± 0.10
9	SD8	1.689 ± 0.11
10	SD9	1.370 ± 0.22
11	SD10	1.047 ± 0.19
12	SD11	1.628 ± 0.21
13	SD12	1.168 ± 0.33
14	SD13	1.132 ± 0.14
15	SD14	1.813 ± 0.43
16	SD15	1.473 ± 0.14

*n= SD ± 3

% Practical yield and drug content

The results of % practical yield and % drug content were summarized in Table 4. Formulation SD14 was found to be highest % practical yield and % drug content of 98.34 ± 0.45% and 99.66 ± 0.50% respectively when compared with other formulations.

In vitro dissolution studies

The drug release data obtained for formulations SD1-SD15 are tabulated in Table 5, 6 & 7. It shows the cumulative percent drug released as a function of time for all formulations. The cumulative percent drug released after 90 min was shown in table. In vitro studies reveal that there is marked increase in the

dissolution rate of Nebivolol from all the solid dispersions when compared to pure Nebivolol itself. From the in vitro drug release profile, it can be seen that formulation SD14 containing Kleptose HPB and SLS (1:5:2 ratio of drug: Polymer with surfactant) shows higher dissolution rate i.e. 98.17 ± 5.39% compared with other formulations. This may be attributed to the increase in drug wettability, conversion to amorphous form and solubilization of the drug due to hydrophilic carrier. The graphical representation of solid dispersions of SD1- SD15 with pure drug was depicted in Figures 4, 5 & 6.

Table 4: % Practical yield and drug content for Nebivolol solid dispersions

S. No	Formulation	% Practical Yield	% Drug content
1	SD1	91.15 ± 0.10	93.12 ± 0.20
2	SD2	93.36 ± 0.20	92.34 ± 0.15
3	SD3	92.24 ± 0.15	95.56 ± 0.30
4	SD4	96.14 ± 0.35	97.44 ± 0.40
5	SD5	95.27 ± 0.30	96.35 ± 0.35
6	SD6	94.36 ± 0.25	91.66 ± 0.10
7	SD7	93.09 ± 0.20	90.71 ± 0.05
8	SD8	90.36 ± 0.05	93.24 ± 0.20
9	SD9	92.33 ± 0.15	94.36 ± 0.25
10	SD10	91.29 ± 0.10	95.12 ± 0.30
11	SD11	93.46 ± 0.20	97.07 ± 0.40
12	SD12	94.31 ± 0.25	98.23 ± 0.45
13	SD13	95.29 ± 0.30	96.42 ± 0.35
14	SD14	98.34 ± 0.45	99.66 ± 0.50
15	SD15	96.23 ± 0.35	94.39 ± 0.25

Table 5: Stability studies of optimized formulation (SD14) stored at 40 ± 2°C / 75 ± 5% RH

Retest time for optimized formulation	% Drug content	In-vitro drug release (%)
0 days	99.66	98.17
30 days	98.24	98.02
60 days	97.89	97.24
90 days	96.42	97.01

Characterization

FTIR Studies

The FTIR spectra of pure Nebivolol, physical mixture and optimized formulation SD14 are shown in Figure 7, 8 and 9 respectively. From Figure 9 it was observed that there were no significant changes in the position of characteristic peaks of the drug when mixed with

carriers which indicated no incompatibility of excipients and the drug.

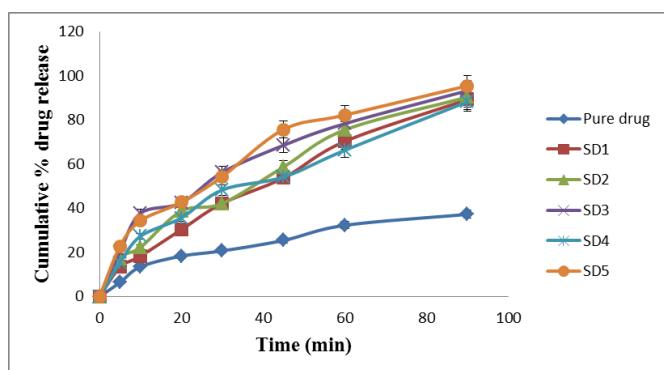


Fig. 4: *In vitro* dissolution profile of pure drug and different formulations of Nebivolol solid dispersions (SD1-SD5)

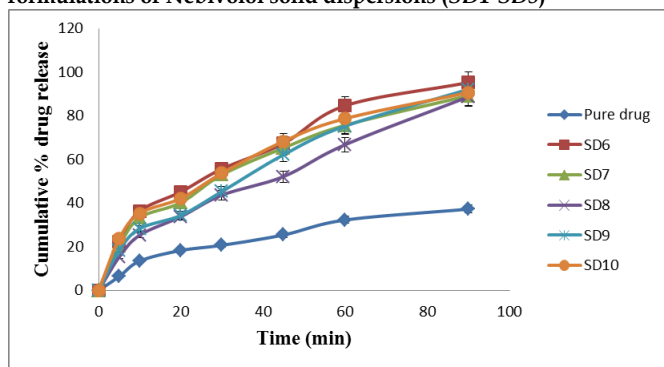


Fig. 5: *In vitro* dissolution profile of pure drug and different formulations of Nebivolol solid dispersions (SD6-SD10)

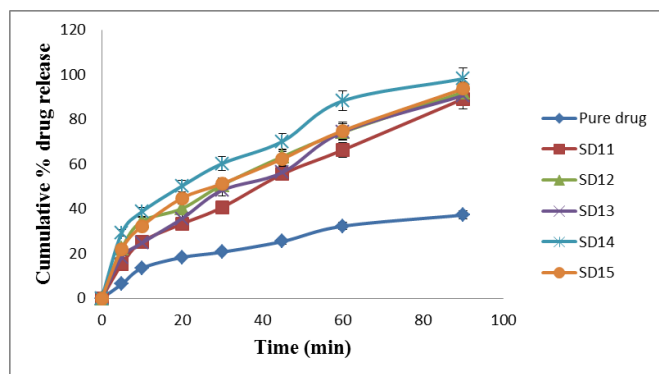


Fig 6: *In vitro* dissolution profile of pure drug and different formulations of Nebivolol solid dispersions (SD11-SD15)

X-Ray Diffraction patterns

The Nebivolol solid dispersions were carried out to find out whether the solid dispersions of various drug polymer ratios are crystalline or amorphous. The presence of numerous distinct peaks in the XRD spectrum of pure Nebivolol indicates that it was present as a crystalline material. On the other hand, the spectrum of optimized formulation SD14 of solid dispersion was characterized by the complete absence of any diffraction peak, which is characteristic of an amorphous compound (Figure 10). The enhancement in the dissolution rate of the drug from the drug- Kleptose HPB and SLS solid dispersion is because of the marked reduction in the crystallinity of the drug.

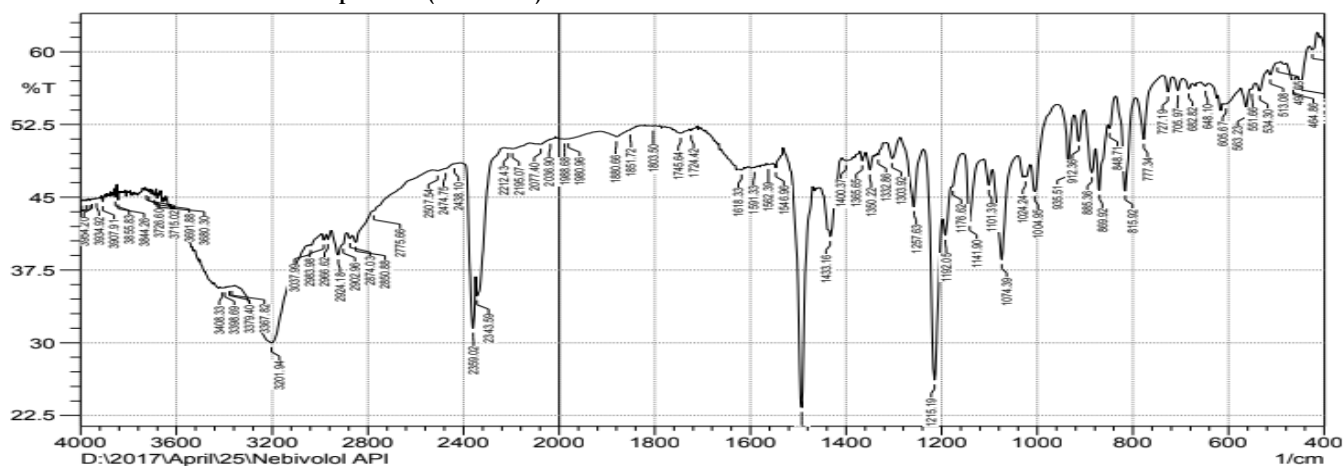


Fig. 7: FTIR Spectrum of Nebivolol pure drug

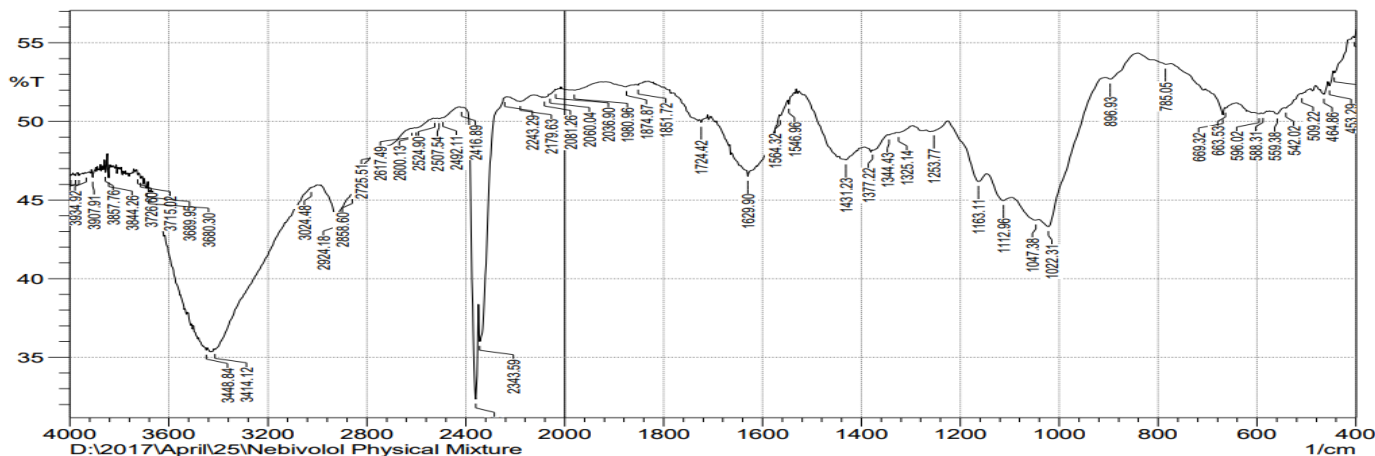


Fig. 8: FTIR Spectrum of Physical mixture

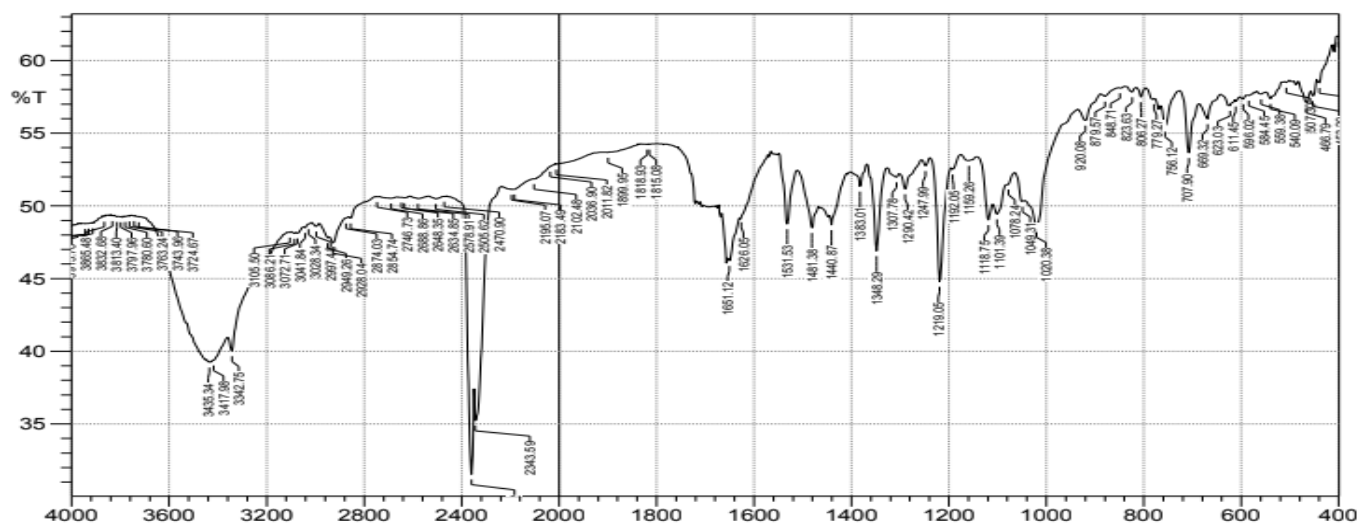


Fig. 9: FTIR Spectrum of Nebivolol Optimized formulation SD14

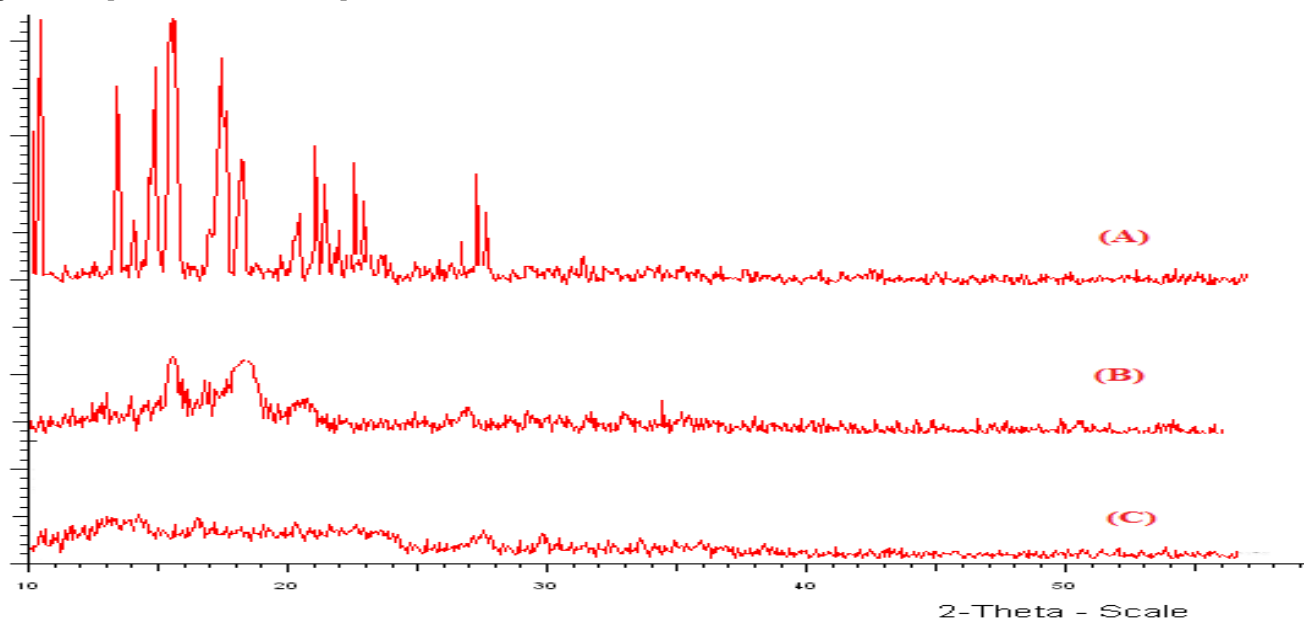


Fig. 10: X-Ray diffractograms of (A) Nebivolol pure drug, (B) Physical mixture, (C) Nebivolol Optimized formulation SD14

SEM Studies

SEM photographs for pure drug and optimized formulation SD14 are shown in Figures 11 & 12. The drug crystals seemed to be smooth-surfaced, irregular in shape and size. In case of Solid dispersions, it was difficult to distinguish the presence of drug crystals. The drug surface in solid dispersion seems to be more porous in nature. Solid dispersions appeared as uniform and homogeneously mixed mass with wrinkled surface. Drug crystals appeared to be incorporated into the particles of the polymers. The solid dispersion looked like a matrix particle. The results could be attributed to dispersion of the drug in the molten mass of the polymer.

Stability studies

Optimized formulation (SD14) was selected for stability studies on the basis of high cumulative % drug release. Stability studies were conducted for drug content and In vitro drug release studies for 3 months at accelerated stability conditions according to ICH guidelines. The optimized formulation was stable during 3months

period. From these results it was concluded that, optimized formulation (SD14) is stable and retained their original properties with minor differences and the results are summarized in Table 5.

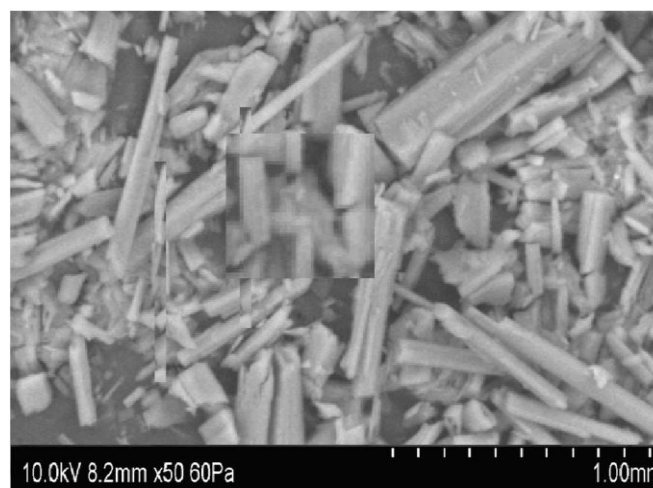


Fig. 11: Pure drug of Nebivolol

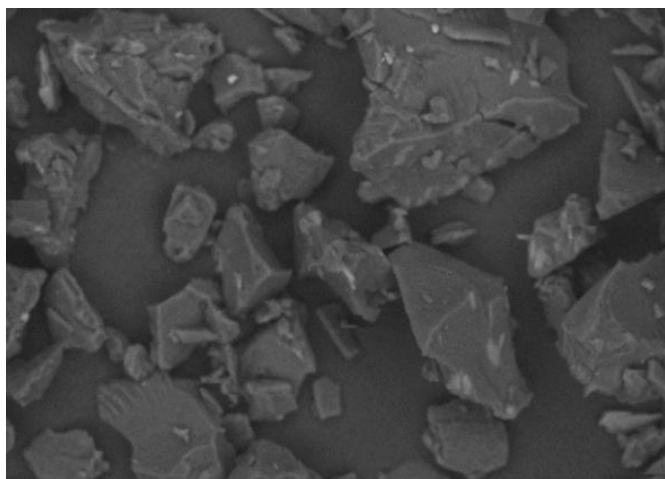


Fig. 12: Nebivolol optimized formulation SD14

The dissolution rate of Nebivolol was increased with solid dispersions prepared by solvent evaporation technique without any physical and chemical interaction. In the present study, fifteen formulations of solid dispersions were prepared with 1:1:1, 1:5:2 and 1:3:1.5 ratios of drug: carrier: surfactant by solvent evaporation method. There was significant improvement in the rate of drug release from all 15 solid dispersions and the formulation (SD14) comprising Nebivolol: Kleptose HPB: SLS in 1:5:2 ratio has shown enhanced solubility about 42 folds and significant improvement in the rate of drug release i.e 98.17 within 90 min when compared with pure drug of 37.24 up to 90 min. From powder X-ray diffraction (p-XRD) and by scanning electron microscopy (SEM) studies it was evident that polymorphic form of Nebivolol has been converted into an amorphous form from crystalline within the solid dispersion formulation. The present study demonstrated that formulation of Nebivolol solid dispersion is a highly effective strategy for enhancing the bioavailability of poorly water soluble drug Nebivolol.

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