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Original Article

ENHANCEMENT OF SOLUBILITY AND DISSOLUTION OF NEBIVOLOL BY SOLID DISPERSION TECHNIQUE

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ABSTRACT

Objective: Solubility is greater challenges for formulation which can be explain by different technological approaches during the pharmaceutical product development and to improve water solubility and drug release respectively.

Methods: The solid dispersions of nebivolol were prepared in ratio 1:1, 1:3, 1:5 and 1:7 by fusion and solvent evaporation method using PEG 6000 and PVP K30 as carriers to enhance solubility of compound.

Results: All the solid dispersions were evaluated for drug content, phase solubility, *in vitro* dissolution study. Deferential Scanning Calorimetric (DSC) and Fourier Transformer Infra Red (FTIR) showed no chemical interaction between the drug and its carriers. Solubility of PEG 6000 and PVP K30 indicates a linear relationship (A_L type of curve) in the investigated polymer concentration range. The Gibb's free energy showed declined trend with increase in the carrier concentrations. The uniformly of drug content was found in all solid dispersions. The drug release obtained from different drug-carrier concentration level fitted to different kinetic model and it was found that solid dispersions exhibited fickian diffusional characteristics and best fitted to higuchi model. A PVP K30 solid dispersion (1:7 ratio) prepared by solvent evaporation method showed faster dissolution rate (94.38 %) in 30 min among studied solid dispersions..

Conclusion: The overall results showed that process of nebivolol transfer from water to carrier solution is more favorable at higher level of PVP K30. The solid dispersion of drug: PVP K 30 (1:7 ratio) prepared by solvent evaporation method was found to be optimum in term of solubility and dissolution rate. Hence, we can concluded that solubility of nebivolol can be enhanced using this carrier ratio.

Keywords: Nebivolol, Solid dispersion, Fusion method, Solvent evaporation method.

INTRODUCTION

Based on the permeability of drug, the Biopharmaceutical Classification System (BCS) categorizes into two major classes, viz. Class II and IV. Drugs which belong to class II of the biopharmaceutical classification system (BCS) are characterized by high membrane permeability and slow dissolution rate (due to low aqueous solubility) [1]. The solubility or dissolution rate of a drug in this category is therefore a key factor in determining the rate and extent of its absorption.

Enhancement of the dissolution rate is essential to obtain for therapeutic effect and rate-limiting step for bioavailability. Several technological methods have been reported for improvement of solubility and dissolution rate of poorly water-soluble drugs, namely reducing particle size, solubilization in surfactant systems, formation of water soluble complexes, strong electrolyte salt formation that usually have higher dissolution rates[2], manipulation of the solid state of the drug substance to improve drug dissolution[3].

Solid dispersion can be defined as distribution of active ingredients in molecular, amorphous, and/or crystalline forms surrounded by an inert carrier [4-5]. Formulation of poorly water-soluble drugs as solid dispersions leads to a marked improvement in their dissolution rates and is often helped by an increase in their relative bioavailability [6-7].

Nebivolol is a beta-adrenergic receptor blocking agent, having very low water solubility, which results into poor dissolution rates. The main objective of this work was to investigate the possibility of improving the solubility and dissolution rate of NEB by preparing solid dispersions with various carriers by two different methods viz. fusion method and solvent evaporation method. Solid dispersions were evaluated for solubility studies, *in-vitro* dissolution rate studies and interaction between drug and carriers using FT-IR, DSC, SEM studies.

MATERIALS AND METHODS

Materials

Nebivolol HCl was kindly gifted by Glenmark Generics Limited (Colvale) Goa. PEG 6000, PVP K 30 and methanol were obtained from CDH Delhi.

Phase solubility study

Phase solubility studies were carried out to evaluate the possible solubilizing effect of the carrier by adding an excess amount of drug to flask containing 10 ml of aqueous solutions containing increasing concentrations of PEG 6000 and PVP K 30 (0.1–1% w/v). The flasks were placed in a mechanical shaker at 300 rpm and room temperature for 24 hour. After 24 hour these solutions were filtered and analyzed by UV spectrophotometer.

The apparent stability constant (K_s) was calculated according to the following equation [8]

$$Ks = \frac{\text{Slope}}{\text{Intercept } (1-\text{Slope})} \quad \ldots\ldots\ldots\ldots (1)$$

The Gibbs free energy of transfer (ΔG^0_{tr}) of nebivolol from pure water to the aqueous solution of carrier was calculated as follows:

$$\Delta G^0 = -2.303RT \log \frac{So}{Ss} \quad \ldots\ldots\ldots\ldots\ldots\ldots (2)$$

Where S_0/S_S is the ratio of molar solubility of nebivolol in aqueous solutions of carrier to that of the same medium without carrier

Determination of saturation solubility [2]

Solubility study was performed using agitation method and saturated solution of nebivolol was prepared in respective solvent media and stirred for 24 hours. The solution was then centrifuged for 15 min over 10,000 rpm and filtered through whatmann filter paper 0.45 mm. The concentration of nebivolol was determined

using UV-visible spectrophotometer (UV-1800, Shimadzu corporation) against respective solvent as blank.

Preparation of solid dispersions

Fusion method [9]

Solid dispersion was prepared by melting the weighed amount of either of the different carriers separately in a glazed porcelain evaporating dish. The carrier was heated to a temperature just sufficient to melt it completely. The drug was then added to this melt, mixed thoroughly and continuously until a uniform mix is obtained where upon the dish was instantly removed from the heat source, and immediately cooled to 5°C using ice water mixture. The dish was maintained at the specified temperature for period of 5 minutes or so until solidified hard mass remained. Then allowed to air dry at room temperature for 48 hr with intermittent mixing and agitation. The dispersions after drying were pulverized using a glass mortar and pestle. The pulverized mass was then sifted through a #40 sieve to obtain a uniform particle size and stored in desiccators at room temperature until further use. The dispersions were prepared in different ratios with respect to drug and polymers as shown in Table 1.

Solvent evaporation method [10]

Solid dispersions were prepared by dissolving weighed amount of either of the different carriers separately in a glazed porcelain evaporating dish in a quantity of methanol sufficient to dissolve it completely. The drug was then added to this solution and mixed thoroughly and continuously until the major portion of methanol used was volatilized and hard to semisolid mass remained. Then allowed to air dry at room temperature for 48 hr with intermittent mixing and agitation.

The dispersions after drying were pulverized using a glass mortar and pestle. The pulverized mass was then sifted through a #40 sieve to obtain a uniform particle size and stored in desiccators at room temperature until further use. The dispersions were made in different ratios with respect to drug and polymers as shown in Table 1.

Table 1: Composition of solid dispersion

Formulation code	Carrier	Drug: carrier	Method
F1	PEG 6000	1:1	Fusion method
F2		1:3	
F3		1:5	
F4		1:7	
F5	PVP K 30	1:1	Solvent evaporation
F6		1:3	
F7		1:5	
F8		1:7	

Solid state characterization

Fourier Transform Infrared Spectroscopy (FTIR)

FT-IR spectrum of the pure drug sample was recorded with Shimadzu 8400S. The interference study was carried out using FTIR analysis. IR spectrum of pure drug, pure polymer and its solid dispersions were performed for polymer drug interaction studies between 4000 $cm^{-1}$to 400 cm^{-1}.

Differential scanning calorimetric analysis (DSC)

The possibility of any interaction between the drugs and the carriers during different approaches was assessed by carrying out thermal analysis of drug as well as the optimized formulation, using DSC. DSC analysis was performed using Shimadzu-Thermal Analyzer DSC 60 (Japan) on 1 to 5 mg samples. Samples were heated in an open aluminum pan at a rate of 10°C/min conducted over a temperature range of 50 to 300°C under a nitrogen atmosphere.

Scanning electron microscopy (SEM)

Morphology of prepared solid dispersion were examined by scanning electron microscope (JSM-5610, Tokyo, Japan) operating at 10.0 kV accelerating voltage. For conventional imaging in the SEM, specimens must be electrically conductive, at least at the surface, and electrically grounded to prevent the accumulation of electrostatic charge at the surface. Therefore the optimized solid dispersions were carbon coated before being subject to electron scanning. The energy of electron beam was set at 10 kV.

***In-vitro* drug release/dissolution studies**

The *in vitro* dissolution study was performed in a USP Type II dissolution test apparatus using 900 ml of phosphate buffer (pH 6.8) at 37+0.5 °C and stirred at 50 rpm for 30 min. Pure nebivolol or its equivalent of SD was sprinkled into the dissolution flask. At predetermined time intervals, samples of the dissolution medium were withdrawn, filtered through a millipore membrane of 0.45 mm pore diameter and analyzed spectrophotometrically against a blank formulation.

Drug content uniformity [2]

Sample containing 10 mg of prepared solid dispersion was accurately weighed and dissolved in freshly phosphate buffer pH 6.8 in a 100 ml volumetric flask. Then the volume was made up to 100 ml with phosphate buffer pH 6.8. From this 1 ml was taken and suitable dilutions were made to get 1 µg/ml with phosphate buffer pH 6.8. The absorbance of the resulting solution was measured at 280 nm against blank (phosphate buffer pH 6.8).

Mathematical models for drug release kinetics

The *in vitro* drug release data were fitted to various release kinetic models [11-14] viz. first-order, Higuchi, Hixson-Crowell cube root, Korsemeyer–Peppas and zero-order model employing the following set of equations:

First-order model

$$ln\frac{Mo}{Mt} = k_1 t \quad \text{..... (3)}$$

Zero-order kinetic model

$$M_0 - M_t = k_0\, t \quad \text{.....(4)}$$

Higuchi model

$$M_t = K\sqrt{t} \quad \text{..... (5)}$$

Hixson-Crowell cube root model

$$\sqrt[3]{W_0} - \sqrt[3]{W_t} = \sqrt[3]{k}\, t \quad \text{..... (6)}$$

Korsemeyer–Peppas model

$$\frac{M_t}{M_\infty} = kt^n \quad \text{..... (7)}$$

Where M_o, M_t and M_∞ correspond to the drug amount taken at time equal to zero, dissolved at a particular time t and at infinite time, respectively. The terms W_o and W_t refer to the weight of the drug taken initially and at time t, respectively. Various other terms viz. k, ko, k_1, $k_{1/3}$ and K refer to the release kinetic constants obtained from the linear curves of Korsemeyer–Peppas, zero-order, first-order, Hixson-Crowell cube root law and Higuchi model, respectively [15].

Statistical analysis [16]

All the results were expressed as mean value ± standard deviation (SD). One way analysis of variance (ANOVA) by using graph pad prism 6 XML was used to test for significance, at a 0.5% significance level. Statistical difference dealing ($P < 0.05$) was considered significant.

RESULTS AND DISCUSSION

Phase solubility study: Fig. 1 represents solubility of PEG 6000 and PVP K30 indicates a linear relationship (A_L type of curve) in the investigated polymer concentration range. The Gibb's free energy of

transfer (ΔG^0_{tr}) and apparent stability constants (K_s) derived from Fig. 1 are shown in Table 2. The plots of drug solubility against the polymer concentration (Fig. 1) Table 2 show that all values of ΔG^0_{tr} were negative at all levels of carriers, demonstrating spontaneity of drug solubilization process. The values show a declining trend with increase in the carrier concentration to construing that the process is more favorable at higher carrier levels. Table 2 also indicates that PVP K30 interaction has a higher K_s value. The higher K_s value indicates that the binding affinity between PVP K30 is more than that of PEG 6000. The results show that in both cases, the solubility of PVP K 30 increased with increasing carrier concentration.

Table 2: Gibbs free energy values and apparent stability constants (Ks) of PVP K30 and PEG 6000 interactions

Concentration of carrier (%w/v)	G°_{tr}(j/mol) for various water-soluble carriers at 37°C	
	PEG 6000	PVP K 30
0.1	-79.37	-250.74
0.25	-154.20	-458.47
0.50	-394.14	-971.68
0.75	-663.59	-1214.91
1	-835.17	-1532.25
Slope	0.680	0.985
k_s	17.8571	564.327
R^2	0.903	0.960

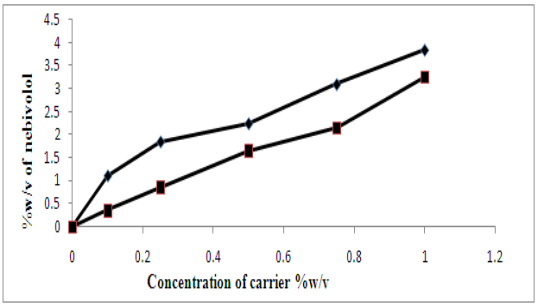


Fig. 1: Solubility of nebivolol (g/100 ml) in aqueous solutions of PVP K30 and PEG 6000 in water at 37°C. (Each point represents mean of three determinations.)

Saturation solubility

Saturation solubility of nebivolol was determined in various aqueous media (distilled water, 0.1 N HCL, phosphate buffer pH 6.8 and methanol). In acidic pH, nebivolol has appreciable solubility owing to its ionization and basic nature. It is obvious that it dissolves less in the solutions of higher pH in which it remains in a unionized form. From the solubility study data nebivolol shows lower solubility in water.

Table 3: Solubility study data

S. No.	Solvent media	Concentration (mg/ml)
1	0.1N HCL	0.215
2	pH 6.8 phosphate buffer	0.115
3	Water	0.041
4	Methanol	0.569

Fourier Transform Infrared Spectroscopy (FTIR) analysis

Fig. 2-6 shows the FTIR spectrum of NEB and its optimized solid dispersions. Characteristic peaks of NEB at 1595.02 cm-1 (N-H stretching), 3203.54 cm-1 (O-H stretching), and 1101.20 cm-1 (cyclic ether C-O stretch), 3003.01 cm-1(aryl substituted C=C), 1303 cm-1 (C-N stretch) and 2923.88 (C-H stretch) were observed. Important vibrations in the spectrum of PEG 6000 are the OH stretching at 3442.70 cm-1 and C–H stretching at 2887.24 cm-1. The spectra of PEG6000 (MA 1:1) solid dispersion (Fig. 4) can be simply regarded as the superposition of NEB. The intensities of some peaks in PEG had doubled in its solid dispersion indicating the summation of intensities of drug and carrier at these peaks and probably a slight increase in the crystallinity of PEG.

This slight increase in crystallinity of PEG might be a reason for decrease in solubility with increase in PEG concentration. Slight difference was seen in the position of the absorption bands of PEG whereas the minor peaks due to NEB were absent indicating trapping of NEB inside the PEG matrix. However, the major characteristic peaks for NEB were still present. Important vibrations in the spectrum of PVP K30 (Fig. 5) are the C-N stretching (tertiary amide) at 1541.02 cm−1, C –H stretching at 2954.74 cm−1, C=O stretching at 1662.52 cm−1and C -C stretching at 1290.29 cm−1.Increase in crystallinity of PVP K30 might be a reason for increase in solubility with increase in PVP K30 concentration.

Slight difference was seen in the position of the absorption bands of PVP whereas the minor peaks due to NEB were absent indicating NEB was dissolved inside the PVP matrix. The major characteristic peaks for NEB were still present. All optimized solid dispersions showed characteristic peaks of NEB drug and carriers. These results indicated that there is no chemical interaction between drug and carrier when formed as solid dispersion.

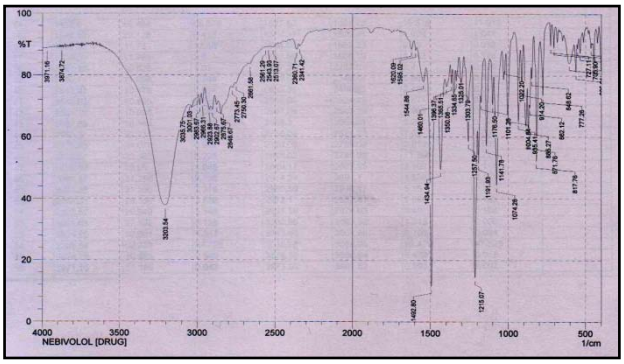


Fig. 2: FT-IR spectra of Nebivolol

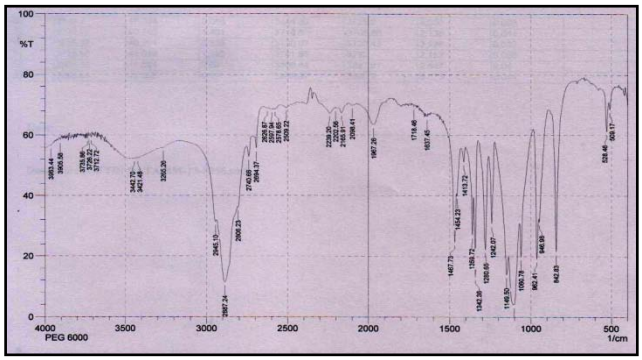


Fig. 3: FT-IR spectra of PEG 6000

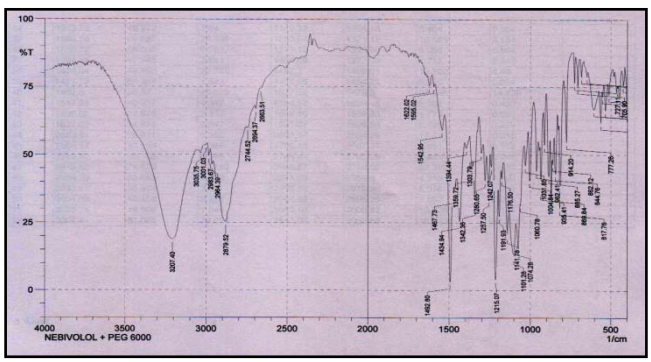


Fig. 4: FT-IR spectra of PEG 6000 SD

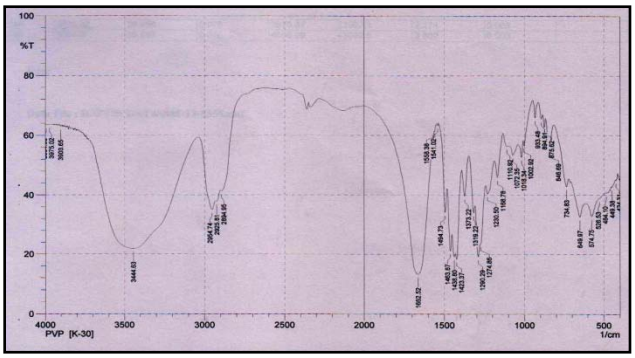


Fig. 5: FT-IR spectra of PVP K30

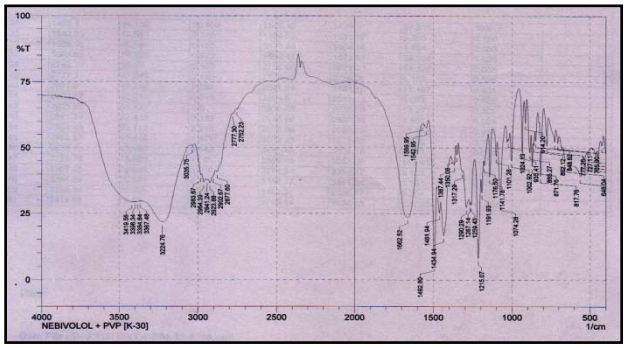


Fig. 6: FT-IR spectra of PVP K30 SD

Differential scanning calorimetric analysis (DSC)

Thermal behavior of pure drug and corresponding drug-carrier system is depicted in (Fig. 7) The DSC curve of NEB profiles a sharp endothermic peak at 228.78ºC corresponding to its melting, indicating its crystalline nature. However, the characteristic endothermic peak, corresponding to drug melting was altered in the optimized solid dispersion. A complete disappearance of the drug melting peak was observed in PVP K30 (SE 1:7) solid dispersion (Fig. 7C) which is attributable to the dissolution of drug in the melted carrier before reaching its fusion temperature whereas one endothermic peak at temperature slightly lower than that of the PVP K30 fusion was observed which may be attributed to the fusion of an eutectic mixture between NEB and PVP K30. It should also be noted that the incorporation of NEB into PVP resulted in a change in the peak temperature of the endotherms displayed by the carrier, indicating that the presence of higher polymer concentration and uniform distribution of drug in the crust of polymer, resulted in complete miscibility of molten drug in polymer. Apart from this, no polymorphic changes were observed in any of the optimized formulations.

Scanning electron microscopy (SEM)

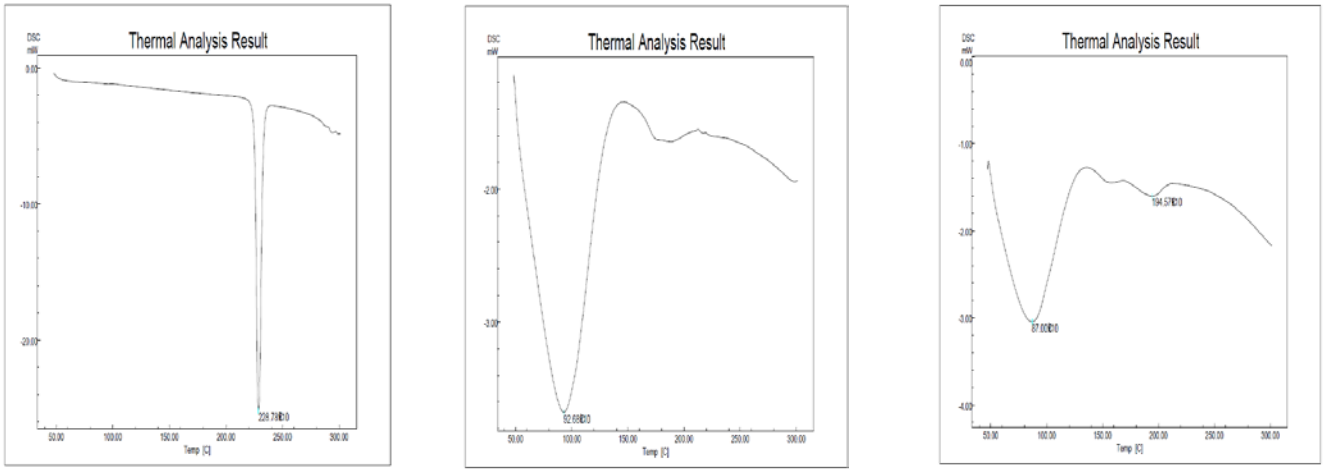
For conventional imaging in the SEM, specimens must be electrically conductive, at least at the surface, and electrically grounded to prevent the accumulation of electrostatic charge at the surface. Therefore the optimized solid dispersions were carbon coated before being subject to electron scanning. The energy of electron beam was set at 10 kV.

Scanning electron micrograph of pure NEB shows needle shaped crystals indicating the crystalline nature of the drug (Fig. 8A). The SEM images of selected solid dispersions are shown in Fig. 8C. SEM photomicrograph of SE PVP 1:7 shows that the drug particles are entrapped within the carrier matrix, confirming FTIR and DSC data analyses. This surface modification ensures the decrease in crystallinity of the drug particle. These images indicate the change in surface morphology of drug particle due to entrapment into the respective polymeric matrix.

***In-vitro* drug release/dissolution studies**

Fig. 9 summarizes the experimentally determined solubility and dissolution of the pure NEB and its solid dispersions in phosphate buffer pH 6.8. All drug-carrier combinations showed an increase in solubility and dissolution of NEB as compared to pure NEB. Amongst, all dispersions PEG 6000 by fusion method and PVP K30 by solvent evaporation method showed an exceptional increase in solubility as well as dissolution of NEB as compared to plain drug. This might be due to hydrophilic nature of the carriers. PEG6000 is a polymer of ethylene oxide and water which entrap NEB into its matrix and enhances the solubility.

Correlating the solubility data with the concentration of carrier with respect to drug, it was observed that with carriers PVP K30, solubility increased with increasing concentration of the carrier whereas with PEG 6000 increase in solubility of NEB was observed with decrease in concentration of carrier. Dissolution profiles of all solid dispersion are shown in fig. 9 which indicated that the SD ratio 1:7 of drug: PVP K30 gives fast dissolution of drug as compared to other ratios. The result of drug release it is concluded that the drug release in following order F8>F3>F4>F7>F6>F2>F5>F1. Fig. 9 showed the dissolution profiles of selected solid dispersions as compared to plain drug.



(A) **(B)** **(C)**

Fig. 7: (A) DSC of nebivolol (B) DSC of PVP K30 (C) DSC of nebivolol with PVP K30

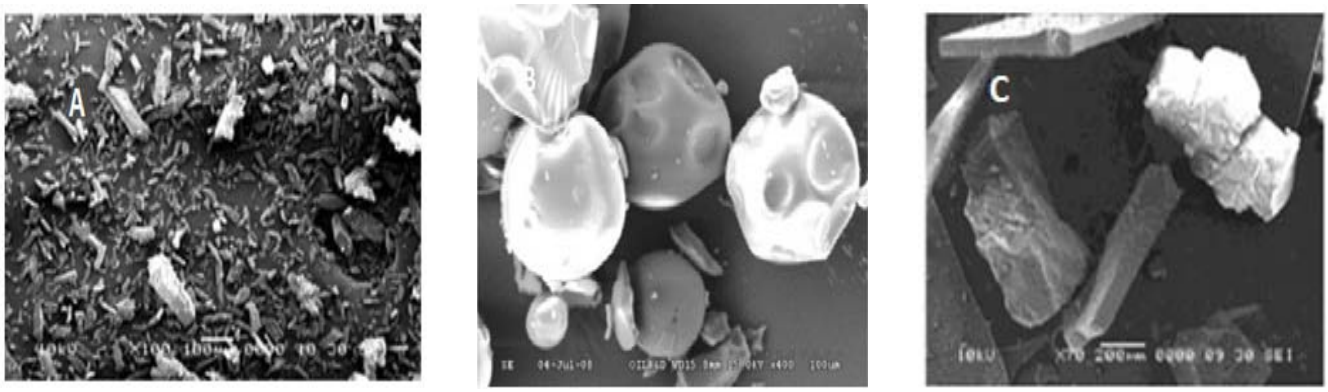


Fig. 8: Scanning electron micrograph of (A) Pure NEB (B) Pure PVP K30 (C) PVP K30 SD

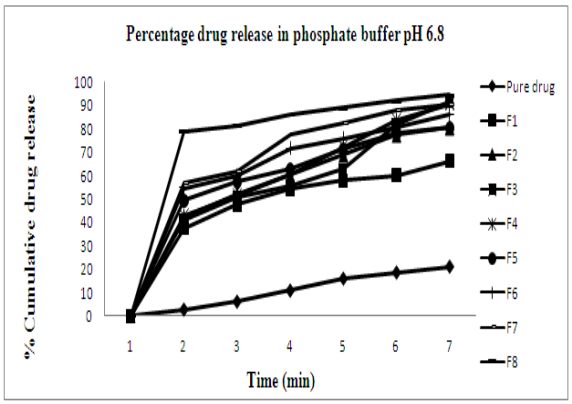


Fig. 9: Dissolution profile of pure nebivolol and their solid dispersion

Drug content uniformity

Drug content of the solid dispersions was found to be between 94.13-97.14 % as shown in table 4. All the solid dispersions showed the presence of high drug content and low standard deviations of the results. It indicates that the drug is uniformly dispersed in the powder formulation. Therefore, the method used in this study appears to be reproducible for preparation of solid dispersion.

Table 4: % Drug content of nebivolol in solid dispersions (mean± S.D)

Batch code	%Drug content
F1	95.84+0.176
F2	96.25+0.028
F3	96.11+0.035
F4	95.52+0.268
F5	95.25+0.042
F6	94.13+0.063
F7	95.55+0.622
F8	97.14+0.042

Mathematical models for drug release kinetics

Solid dispersions of solvent evaporation method tended to exhibit Fickian diffusional characteristics, as the corresponding values of n were lower than the standard value for declaring Fickian release behaviour, i.e., 0.4500. The goodness of fit for various models investigated for binary systems ranked in the order of Higuchi > Korsmeyer-peppas > First-order > zero-order > Hixson-Crowell.

Table 5: Mathematical models for drug release kinetics

Code	Mathematical models for drug release kinetics									
	Zero-order		First order		Hixon-crowell		Higuchi		Korsmeyer-peppas	
	Slope	R^2	Slope	R^2	Slope	R^2	Slope	R^2	Slope	R^2
$(SD)_S$	1.241	0.869	-0.030	0.899	0.111	0.608	15.61	0.970	2.624	0.905
$(SD)_F$	1.249	0.774	-0.034	0.846	0.101	0.430	15.88	0.804	2.263	0.539

$(SD)_S$ = Solid dispersion by solvent evaporation method, $(SD)_F$ = Solid dispersion by fusion method

Statistical analysis

Based on *in-vitro* dissolution performance, the solid dispersion of drug: PVP K 30 (1:7) was showed highest drug release ($P < 0.05$) than compare to other solid dispersions

CONCLUSION

In the present study an attempt was made to enhance the solubility and dissolution of nebivolol. Solid dispersion were prepared using different polymers and by using different methods.

Solid dispersions were further characterized by DSC, SEM and FTIR and it showed that the drug crystallinity was decreases with increase in polymer concentration. Solid dispersions prepared using higher level of PVP K30 (solvent evaporation method) was found to be optimum in terms of drug release. Hence, this method can be used to increase the solubility and dissolution of poorly water soluble drugs.

CONFLICT OF INTERESTS

Declared None

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