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SOLUBILITY ENHANCEMENT OF NEBIVOLOL BY HYDROTROPIC METHOD

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ABSTRACT

Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules. In case of the oral administration solubility is one of the important parameter for achieving desired concentration of drug in systemic circulation for pharmacological response to be shown. Most popular route in drug administration is oral route because of simple, uncomplicated and cost effective administration. There are many advantages of this oral route for hydrophilic drugs but major disadvantage is that lipophilic drugs are poorly insoluble and faces absorption and bio-avaibility issues. Currently, 40% of the drugs are poorly water soluble which produce side effects such as gastric irritation, peptic ulceration etc. whereas only 8% of new drug candidates have shown both high solubility and permeability. Nebivolol is a third-generation beta-a drenoceptor antagonist. It differs from other beta-a drenoceptor antagonists as it combines highly selective beta 1-adrenoceptor antagonist properties with nitric oxide-mediated vasodilator actions and beneficial effects on endothelial function. But this very useful drug use is limited due to challenge of poor water solubility (0.0403 mg/ml). Present study deals with enhancement of solubility of Nebivolol by hydrotropic method.

KEYWORDS: Nebivolol, Solubility enhancement, Hydrotropy method, Dissolution characteristics.

1. INTRODUCTION

Management of hypertension and heart failure with the help of beta-blockers as antihypertensive plays critical role in reduction of cardiac deaths.[1] Novel and highly cardio selective *Nebivolol* is a better beta-blocker in comparison to other beta-blockers and hence more effective and preferred drug.[2] Along with beta blocker effects, *Nebivolol* is vasodilator, anti-atherosclerotic agent and anti *friabilator* agent.[3] Hence, it is very useful antihypertensive drug diabetic and systolic hypertensive patients and with known associated vascular diseases. But the oral administration of drug *Nebivolol* causes gastrointestinal disturbances as well as extensive first pass metabolism and thus faces challenges of poor water solubility and bioavailability.[4] Hence to reduce first-pass metabolism and improve bio availability lipid-based formulation in the form of micro emulsion is prepared and found promising.[5,6]

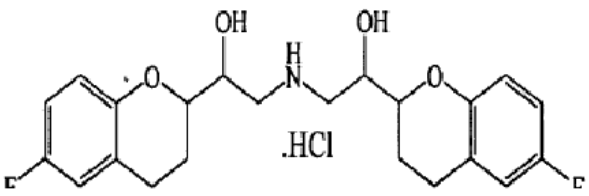


Fig. 1: Structure of Nebivolol hydrochloride

2. MATERIALS & METHODS

Drug and Chemical Reagents

Nebivolol Hydrochlor was purchased from Modern laboratories Pvt. Ltd. Indore, Benzene, Acetic acid, Urea, Sodium acetate, Sodium citrate, Sodium benzoate was purchased from Kashiwal Chemical, Raipur, Chhattisgarh, Diethyl ether, Chloroform, Water, Methanol, Ethanol was purchased from Prism sales, Raipur, Chhattisgarh India. All other chemicals used was of highest analytical grade-commercially available.

METHOD

Hydrotropy

Hydrotropy describes the increase in the solubility of a less soluble solute by the addition of fair concentrations of alkali metal salts of various organic acids. Hydrotropes are the compounds having both an anionic group and a hydrophobic aromatic ring or ring system. Essentially the anionic group increases the hydrophilicity and the ring system interacts with the solute to be dissolved. The term Hydrotropy was coined by Carl Neuberg in 1916[7] but the practical implications were introduced as late as 1976 by Thoma and coworkers. In 1985, Saleh co-workers broadened the virtue of hydrotropic compounds by including the cationic, anionic or neutral molecules having an aromatic ring structure.[8] Hydrotropic polymers were later on added to

the list, Park and coworkers, 2003, 2010, indentified N Picolylnicotinamide (PNA) was one of the best hydrotropes for paclitaxel; N, N diethyl nicotinamide (DENA) and N, N dimethyl benzamide (DMBA) were also used as solubility enhancers.[9,10] *Maheshwari and coworkers* increased solubility of Paracetamol using Urea and of aceclofenac using mixed hydrotropic phenomenon using Urea and Sodium acetate.[11] Sodium acetate was used as a hydrotropic agent to increase the mass transfer coefficient of salicylic acid by Thenesh kumar and co-workers.[12] Hydrotropy has been used by Tambe and coworkers for developing a chromate graphical and spectrophotometric method of estimation of Cefixime.[13] *Pandey and co-workers* used hydrotropic phenomenon of Potassium acetate for analytical estimation of ketoprofen tablet dosage form.[14-16]

Table 1: Various agents used for hydrotropic solubilization of drugs.

S. No.	Drug	Additive used to exhibit Hydrotropism
1.	Cefadroxil	Potassium acetate, potassium citrate, sodium acetate, urea
2.	Paracetamol, Diclofenac Sodium	Sodium Acetate,Urea
3.	Theophylline	Sodium salicylate
4.	Nifedepine	Sodium salicylate
5.	Ketoprofen	Urea, sodium Citrate

3. RESULTS AND DISCUSSION

Table 2: Standard calibration data of nebivolol in 0.1 HCL.

S. No.	Drug Concentration (µg/ml)	Absorbance
1	5	0.094
2	10	0.201
3	15	0.284
4	20	0.395
5	25	0.484
6	30	0.589
7	35	0.664
8	40	0.782

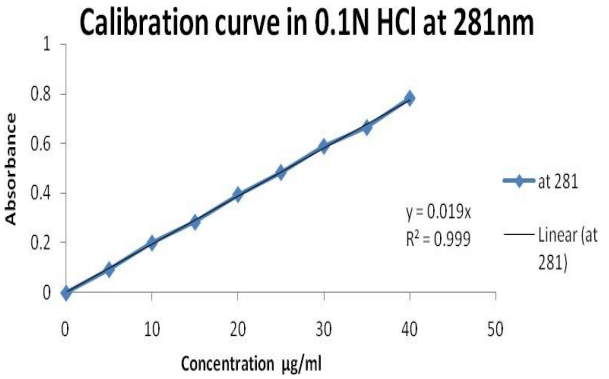


Fig. 2: Calibration Curve in 0.1N HCL at 281nm.

Table 3: Standard Calibration Data of Nebivolol in Methanol.

S. No.	Drug Concentration (µg/ml)	Absorbance
1	5	0.105
2	10	0.221
3	15	0.321
4	20	0.434
5	25	0.533
6	30	0.649
7	35	0.766
8	40	0.839

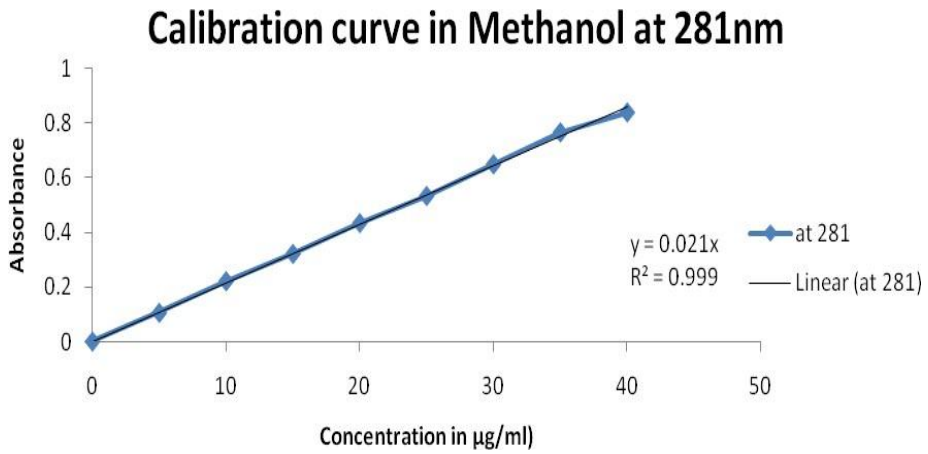


Fig. 3: Calibration curve in Methanol at 281nm.

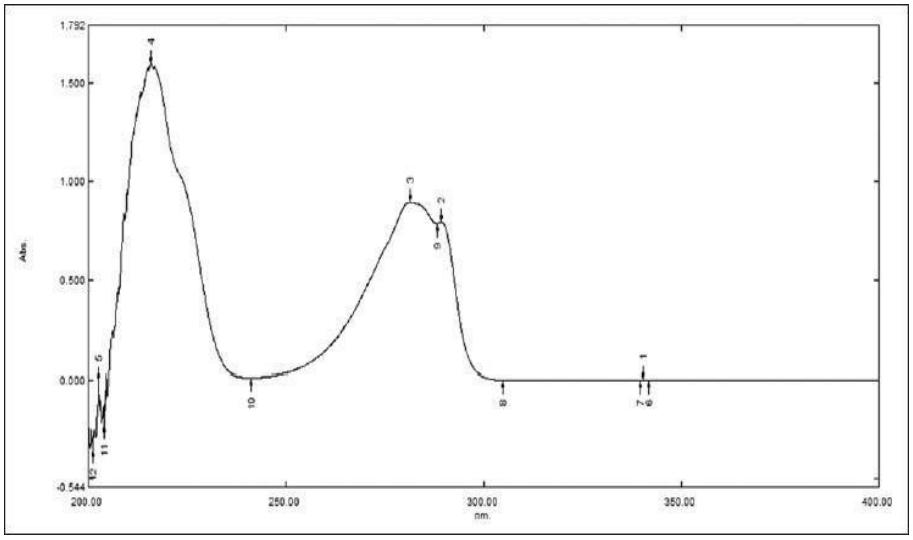


Fig. 4: UV Spectra of Nebivolol.

Solubility determination

Saturation solubility of Nebivolol was determined in various aqueous media (distilled water, 0.1 N HCL, phosphate buffer pH 6.8 and methanol, ethanol, chloroform). 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.

Drug excipients compatibility studies by FT-IR

IR spectra of drug were obtained using FT-IR Drug and excipients were analyzed by IR spectral studies using KBr pellet technique. In this method, the drug and KBr were mixed at the ratio of 1:1. Then these mixtures were pressed in to a pellet. The FT-IR spectra were recorded using KBr pellet method in the region 400-4000 cm-1. Spectra were recorded for pure drug.

Table 4: Solubility determinations.

Solvent	Solubility
Distilled water	Slightly soluble
0.1 N HCL	Sparingly soluble
Phosphate Buffer	Soluble
Methanol	Sparingly soluble
Ethanol	Slightly soluble
Chloroform	Freely soluble

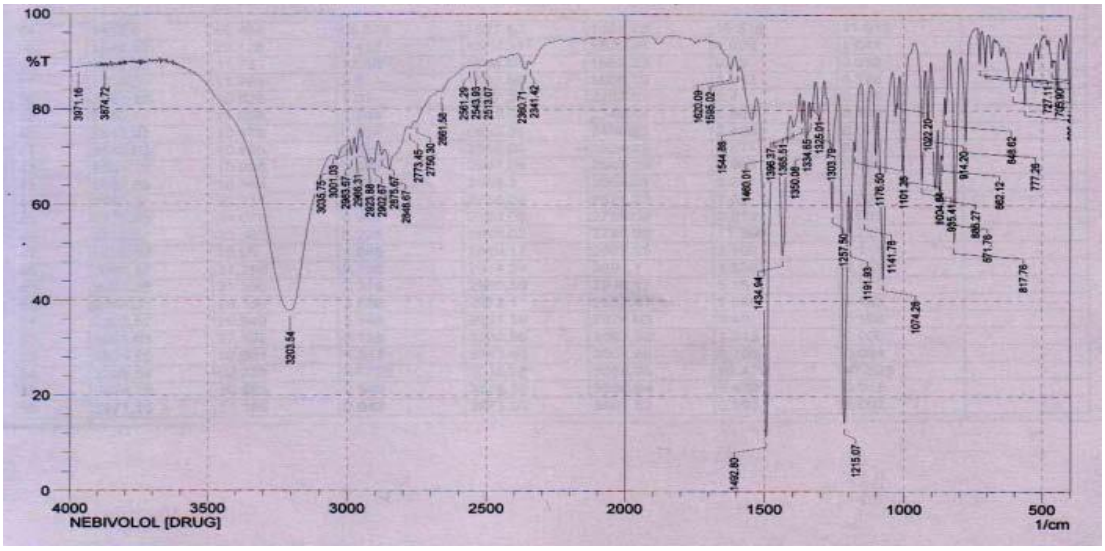


Fig. 5: FT-IR spectra of Nebivolol.

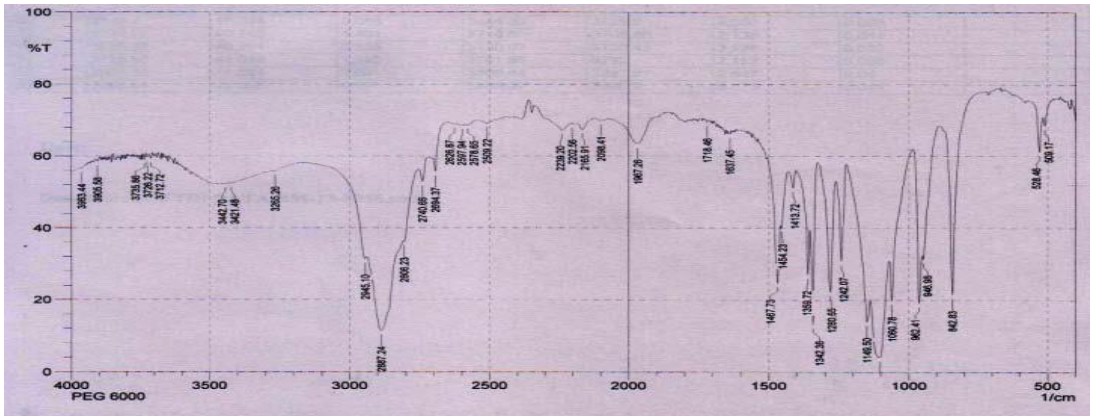


Fig. 6: FT-IR spectra of PEG 6000.

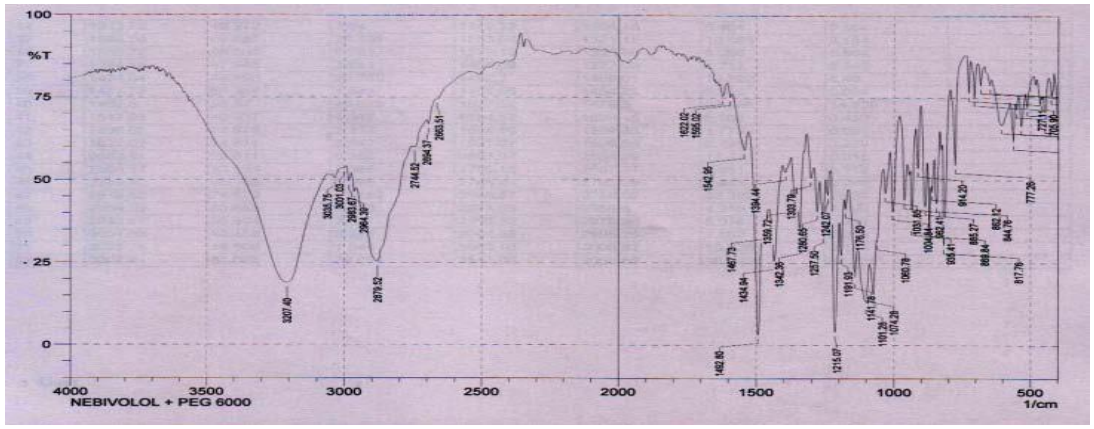


Fig. 7: FT-IR spectra of PEG 6000 SD.

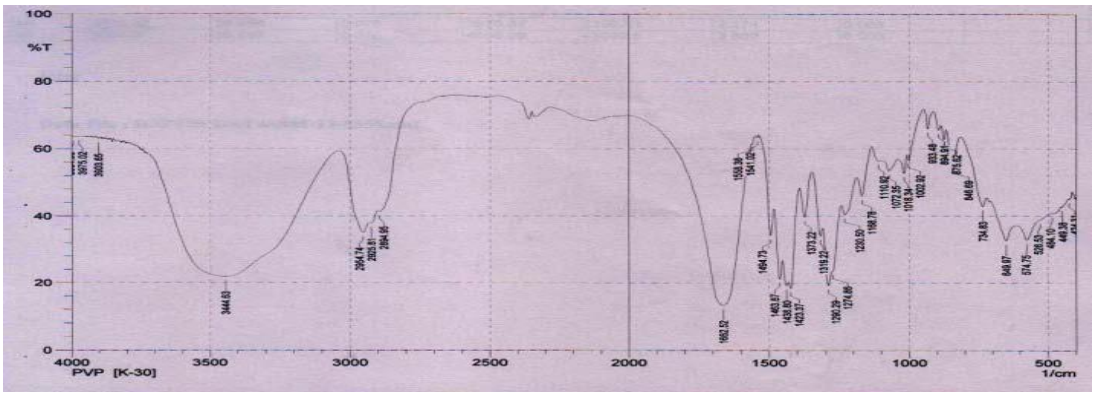


Fig. 8: FT-IR spectra of PVP K30.

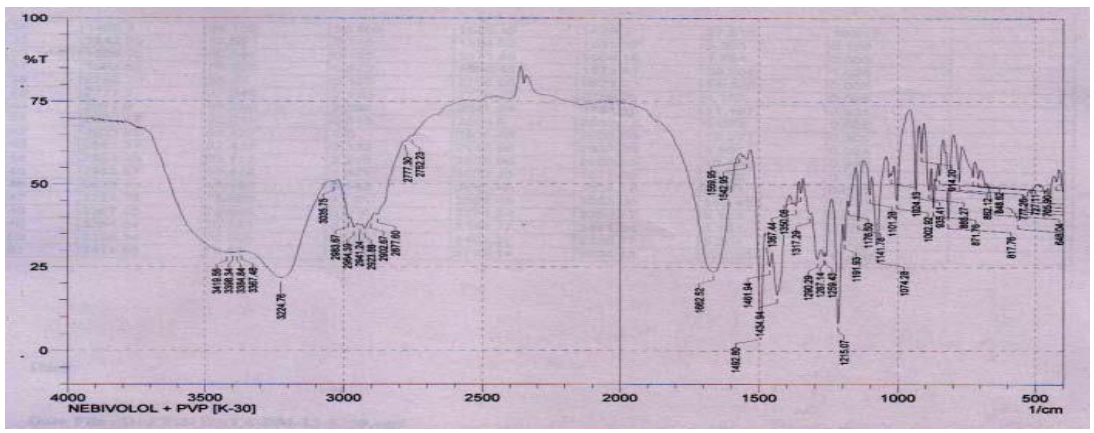


Fig. 9: FT-IR spectra of PVP K30 SD.

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.[17]

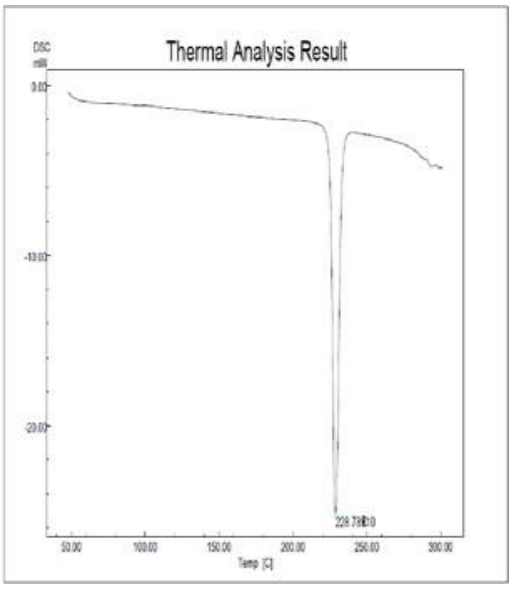


Fig. 10: DSC of Nebivolol.

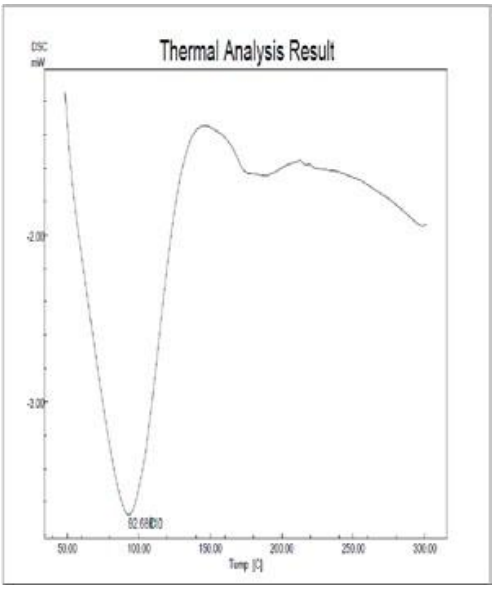


Fig. 11: DSC of PVP K30.

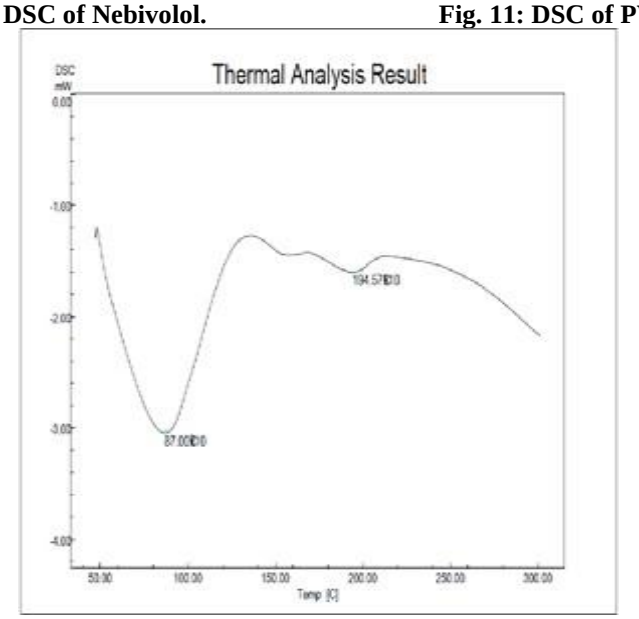
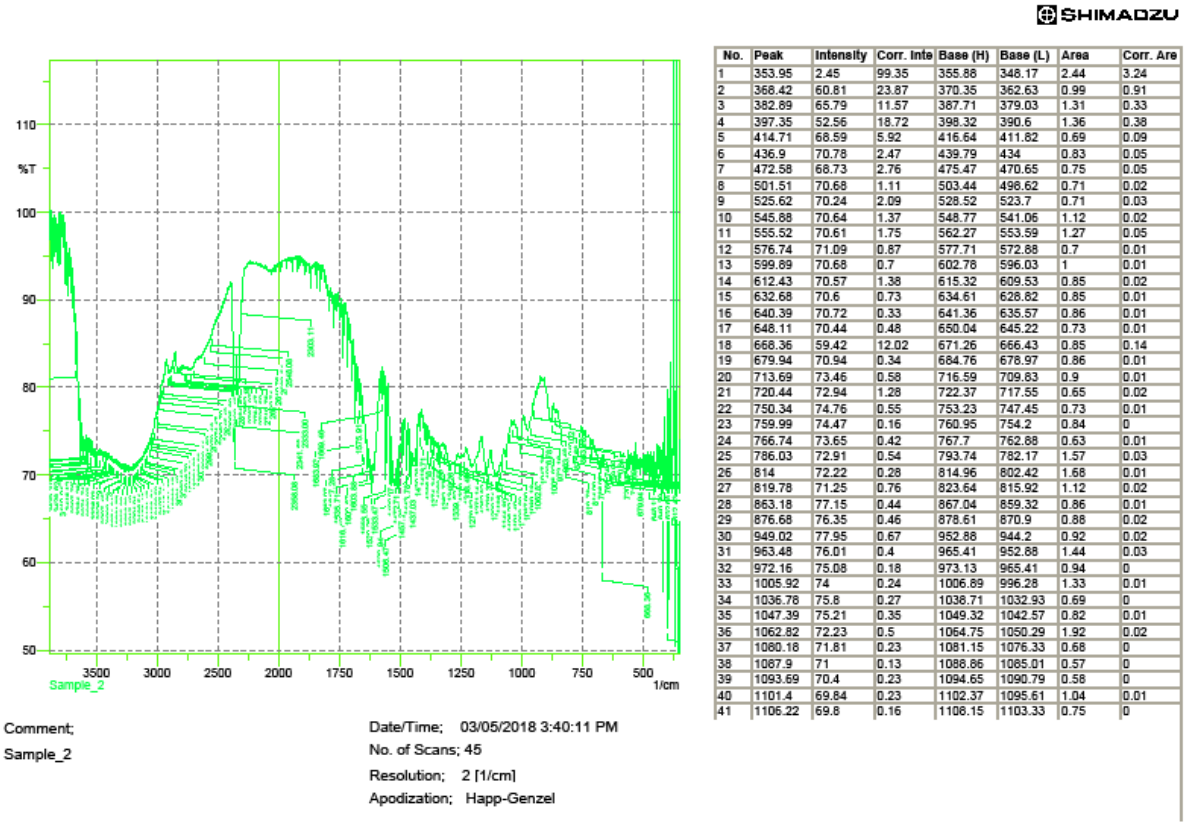


Fig. 12: DSC of Nebivolol with PVP K30Z.

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 -1-1 studies between 4000 cm to 400 cm.[18]



No.	Peak	Intensity	Corr. Inte	Base (H)	Base (L)	Area	Corr. Are
1	353.95	2.45	99.35	355.88	348.17	2.44	3.24
2	368.42	60.81	23.87	370.35	362.63	0.99	0.91
3	382.89	65.79	11.57	387.71	379.03	1.31	0.33
4	397.35	52.56	18.72	398.32	390.6	1.36	0.38
5	414.71	68.59	5.92	416.64	411.82	0.69	0.09
6	436.9	70.78	2.47	439.79	434	0.83	0.05
7	472.58	68.73	2.76	475.47	470.65	0.75	0.05
8	501.51	70.68	1.11	503.44	498.62	0.71	0.02
9	525.62	70.24	2.09	528.52	523.7	0.71	0.03
10	545.88	70.64	1.37	548.77	541.06	1.12	0.02
11	555.52	70.61	1.75	562.27	553.59	1.27	0.05
12	576.74	71.09	0.87	577.71	572.88	0.7	0.01
13	599.89	70.68	0.7	602.78	596.03	1	0.01
14	612.43	70.57	1.38	615.32	609.53	0.85	0.02
15	632.68	70.6	0.73	634.61	628.82	0.85	0.01
16	640.39	70.72	0.33	641.36	635.57	0.86	0.01
17	648.11	70.44	0.48	650.04	645.22	0.73	0.01
18	668.36	59.42	12.02	671.26	666.43	0.85	0.14
19	679.94	70.94	0.34	684.76	678.97	0.86	0.01
20	713.69	73.46	0.58	716.59	709.83	0.9	0.01
21	720.44	72.94	1.28	722.37	717.55	0.65	0.02
22	750.34	74.76	0.55	753.23	747.45	0.73	0.01
23	759.99	74.47	0.16	760.95	754.2	0.84	0
24	766.74	73.65	0.42	767.7	762.88	0.63	0.01
25	786.03	72.91	0.54	793.74	782.17	1.57	0.03
26	814	72.22	0.28	814.96	802.42	1.68	0.01
27	819.78	71.25	0.76	823.64	815.92	1.12	0.02
28	863.18	77.15	0.44	867.04	859.32	0.86	0.01
29	876.68	76.35	0.46	878.61	870.9	0.88	0.02
30	949.02	77.95	0.67	952.88	944.2	0.92	0.02
31	963.48	76.01	0.4	965.41	952.88	1.44	0.03
32	972.16	75.08	0.18	973.13	965.41	0.94	0
33	1005.92	74	0.24	1006.89	996.28	1.33	0.01
34	1036.78	75.8	0.27	1038.71	1032.93	0.69	0
35	1047.39	75.21	0.35	1049.32	1042.57	0.82	0.01
36	1062.82	72.23	0.5	1064.75	1050.29	1.92	0.02
37	1080.18	71.81	0.23	1081.15	1076.33	0.68	0
38	1087.9	71	0.13	1088.86	1085.01	0.57	0
39	1093.69	70.4	0.23	1094.65	1090.79	0.58	0
40	1101.4	69.84	0.23	1102.37	1095.61	1.04	0.01
41	1106.22	69.8	0.16	1108.15	1103.33	0.75	0

Fig. 13: Fourier Transform Infrared Spectroscopy of Nebivolol.

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. Hydrotropic agents was always 40% w/v. The blend U+B+C in the ratio of 15:20:5 gave the highest solubility enhancement, and therefore, this optimized combination of hydrotropes was selected for the preparation of solid dispersions.[19]

Phase solubility study

Fig. 5 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 (ΔG0tr) and apparent stability constants (Ks) derived from Fig. 5 are shown in Table 7. The plots of drug solubility against the polymer concentration (Fig. 5) Table 7 show that all values of ΔG0tr 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 7 also indicates that PVP K30 interaction has a higher Ks value. The higher Ksvalue 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 5: 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	
	PEG6000	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
Ks	17.8571	564.327
R2	0.903	0.960

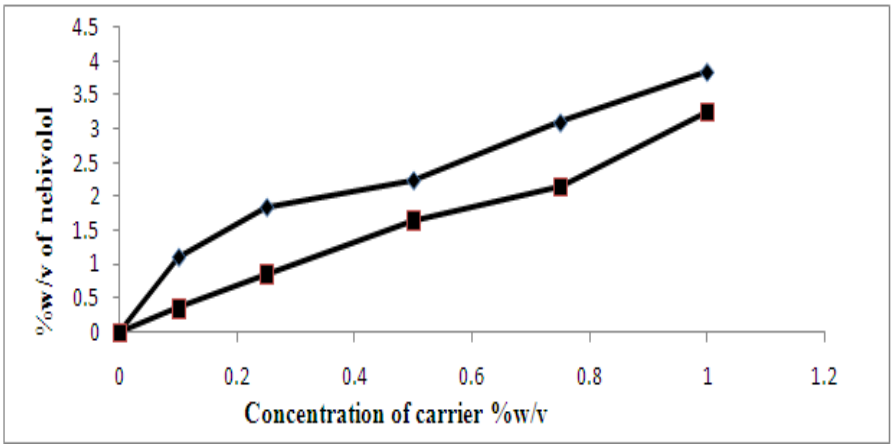


Fig. 14: Solubility of Nebivolol (g/100 ml) in aqueous solutions of PVP K30 and PEG 6000 in water at 37° C. (Each point represents mean of three determinations.).

Dissolution studies

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. 14 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.[20]

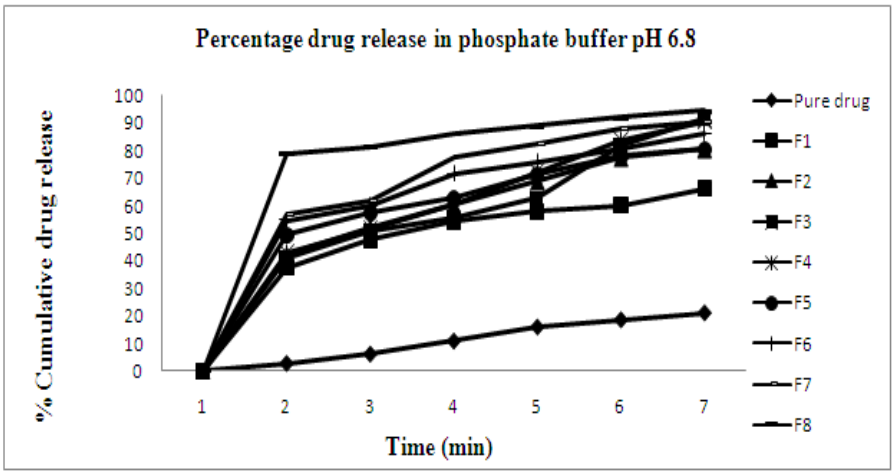


Fig. 15: Dissolution profile of pure Nebivolol and their solid dispersion.

4. EVALUATION PARAMETERS

Dissolution rate studies

Solid dispersion equivalent to 20 mg of Nebivolol were tested in dissolution rate studies using USP XXIV (type II) dissolution test apparatus (Model TDT6P, Electrolab, Mumbai, India) with paddle to rotate at 50 rpm, 900 ml of 0.1N HCl was taken as dissolution media with temperature of 37±0.5°. At definite time interval 10 ml of the sample were withdrawn and were analyzed for drug content. Withdrawn samples were also replaced with fresh dissolution media. Calculations for the amount of drug were done using regression equations. Similarly dissolution of conventional tablet was done.

5. 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 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.

Various technologies have been introduced for the enhancement of solubility of poorly hydrophilic drugs. The basic approaches involve the interaction of a hydrophilic molecule with a poorly soluble drug to give rise a phenomena of increased solubility, which in turn increase the bioavailability and intrinsic activity (pharmacological activity). Older methods had the problem of irregular shape or size, larger particle sizes which to lead to irregular dissolution characteristics or toxicity problems as in case of surfactants. Novel methods have shown the properties of uniform shape and size which when either used in combination or individually will have a potential for the dissolution enhancement of the newer chemical entities to be introduced in the future.

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