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IMPROVEMENT OF SOLUBILITY AND DISSOLUTION RATE OF POOORLY SOLUBLE DRUG CARVEDILOL BY SOLID DISPERSION TECHNIQUE USING COMBINED CARRIERS

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ABSTRACT

In the present study attempt was made to improve solubility and dissolution rate of poorly soluble drug by solid dispersion technique using combined carriers such as poloxamer 188 and PVP K90. Carvedilol is a poorly water soluble oral antihypertensive agent. The Carvedilol belongs to BCS class II drug having low solubility and high permeability. The FTIR study indicates that there is no interaction between drug and polymer. The solid dispersions were prepared by kneading method in three different ratios viz.1:1, 1:2, and 1:4. The prepared solid dispersions were evaluated for solubility study, drug content, and *in-vitro* dissolution study. The prepared dispersion showed marked increase the saturation solubility and dissolution rate of Carvedilol than that of drug alone. The dispersion with poloxamer 188 (1:4) showed High solubility and faster dissolution rate as compared to the other prepared dispersions.

Key words: Carvedilol, solid dispersion, water soluble carrier, Poloxamer 188.

INTRODUCTION

Nearly about 40% of the newly discovered drugs are lipophilic and failed to reach market due to the poor water solubility. [1] Solubility and dissolution rate is the rate determining step for bioavailability of the BCS class II drugs. The bioavailability problem of the BCS class II drugs can be overcome by increasing the solubility and dissolution rate of the drug in the gastrointestinal fluids. [2]

The enhancement of oral bioavailability of poorly soluble drugs is an important aspect of drug development. A poorly soluble compound is defined as one dissolving in less than 1 part per 10,000 of water. It takes more time to dissolve in gastrointestinal fluids than it takes to be absorbed in the gastrointestinal tract. [3]

There were several ways in which bioavailability of the drug can be enhanced all of which aimed at increasing the surface area of the drugs which includes. Micronization, use of salt form, use of metastable polymorphs, solvent deposition, selective adsorption on insoluble carriers, solid dispersion, solute solvent complexation, complexation with cyclodextrins**.** The most promising method for promoting dissolution is the formation of solid dispersion in a proper carrier. The term solid dispersion refers to the dispersion of one or more active ingredients in an inert carrier or matrix in solid state prepared by melting (fusion), solvent, or melting solvent method. Solid dispersions (SDs) have traditionally been used as an effective method to improve the dissolution properties and bioavailability of poorly water-soluble drugs. In solid dispersion systems, a drug may exist as an amorphous form in polymeric carriers, and this may result in improved solubility and dissolution rates as compared with crystalline material. Drugs molecularly dispersed in polymeric carriers may achieve the highest levels of particle size reduction and surface area enhancement, which result in improved dissolution rates. Furthermore, no energy is required to break up the crystal lattice of a drug during dissolution. Process and drug solubility and wettability may be increased by surrounding hydrophilic carriers. [4, 5, 6,]

Carvedilol (CAR), an antihypertensive agent, is used in the treatment of hypertension, congestive heart failure, cardiac arrhythmias and angina pectoris. It is a nonselective β-adrenergic blocker with selective α-adrenergic blocking. Carvedilol is poorly flowable and compressible drug. Being categorized as class II compound as per the BCS classification system, it posses very poor bioavailability and shows significant first pass metabolism [7. 8, 9, 10, 11,]

Carvedilol (CRL), is chemically (±)-1-(Carbazol-4-yloxy)-3-[2-(o-methoxyphenoxy) ethyl] amino]-2-propanol. It is a white to off-white powder with a molecular weight of 406.5. It is freely soluble in dimethylsulfoxide, soluble in methylene chloride and methanol, sparingly

soluble in 95% ethanol and isopropanol, slightly soluble in ethyl ether and practically insoluble in water, [12]

MATERIAL AND METHODS

Carvedilol was supplied by Alkem laboratories Ltd, Mumbai, Poloxamer 188 was obtained as gift sample from Signet chemical corporation Pvt Ltd worli Mumbai, and PVP K90 was obtained as gift sample from Alkem labs Ltd. All other chemicals and reagents and solvent used were of analytical grade.

METHODS

Kneading method for preparation of solid dispersion

Drug (Carvedilol) and hydrophilic polymers (poloxamer 188 and PVP K90) were weighed in different ratio 1:1, 1:2 and 1:4 and triturated in a mortar with a small volume of a solvent blend of water: methanol (1:1). The thick slurry formed was Kneaded for 45 min and then dried at 55ºC until dry. The dried mass was powdered and sieved through mesh No. 120.

Scanning of Carvedilol in 0.1 N HCl

The solution containing 10 µg/ml of Carvedilol was prepared and scanned over range of 200 to 400 nm against 0.1 N HCl as a blank using UV spectrophotometer.

Standard Calibration Curve of Carvedilol in 0.1 N HCl

Stock solution was prepared by dissolving 100 mg of accurately weighed Carvedilol in 100 ml of methanol to get 1 mg/ml solution. Further 10 ml of this solution was pipette into 100 ml volumetric flask and made up to 100 ml with 0.1 N HCl to get 100 µg/ml solutions. Further 10 ml of this solution was pipette into 100 ml volumetric flask and made up to 100 ml with 0.1N HCl to get 10 µg/ml solutions. From this, 0.2,0.4, 0.8.....1.4 ml solutions were pipette into a series of 10 ml volumetric flask and were made up to 10ml with 0.1N HCl to get 2, 4, 6, 8 10 12 and 14 µg/ml solutions of Carvedilol respectively. The absorbance of resulting solutions was measured at 241 nm against the blank. A graph was plotted by taking concentration on X-axis and absorbance on Y-axis.

Characterization of solid dispersion

Flow properties

1) **Bulk density** [13]

Bulk density is defined as the mass of a power divided by the bulk volume. Procedure: - A

sample of solid dispersion was introduced into graduated cylinder. The volume of material was noted on graduated cylinder. The bulk density was calculated by the formula,

$$\text{Bulk density } (\rho) = \frac{\text{Mass of powder (w)}}{\text{Bulk Volume (Vb)}}$$

2) Tapped density

A sample of solid dispersion was filled in graduated cylinder and then tapping was done 100 times initially and the tapped volume (Va) was measured to nearest graduated unit. The tapped density was calculated by the formula,

$$\text{Tapped density} = \frac{\text{Mass of powder (gm)}}{\text{Tapped volume (ml)}}$$

3) Hausner's ratio

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

4) Compressibility Index (%)

The compressibility index and Hausner's ratio are measures of the propensity of a powder to be compressed. Compressibility index of powder was calculated by the formula,

$$\text{Compressibility} = \frac{\text{Tapped density-Bulk density}}{\text{Tapped Density}} \times 100$$

Solubility study

Solubility measurements of Carvedilol were performed according to a published method. Solid dispersions equivalent to 100 mg of Carvedilol was shaken with 10 ml distilled water in stopper conical flask in an orbital shaker for 24 hours at room temperature. Subsequently, the solutions were filtered through a Whatman filter paper no 1. Filtered solution was diluted properly with 0.1N HCl. The diluted solution was analyzed for the Carvedilol in UV at 241 nm. Solubility of each sample was determined in triplicate. Results are shown in table No.3 [14]

Drug content

Solid dispersions equivalent to 10 mg of Carvedilol were weighed accurately and dissolved in the 10 ml of methanol. The solution was filtered, diluted suitably and drug content was analyzed at 241 nm by UV spectrophotometer ((UV-visible Spectrophotometer- Shimadzu UV 1800). The Actual Drug Content was calculated using the following equation as follows:

%Drug content = (Mact/Mt) X 100

Mact = Actual amount of drug in Solid dispersion

Mt = Theoretical amount of drug in solid dispersion

Dissolution study

In vitro dissolution study was performed in a paddle type dissolution apparatus (USP apparatus II). Accurately weighed solid dispersion containing 25 mg Carvedilol from each batch were used for dissolution study. 0.1 N hydrochloric acid solution was used as dissolution medium at a temperature of 37 ± 0.5° C and a paddle speed was 50 rpm. Dissolution study was carried out for 60 min and 5 ml sample was withdrawn at predetermined intervals of 5, 10, 15, 20, 30, 40, 50 & 60 min. The sink condition was maintained by adding 5 ml fresh medium every time. Dissolution samples were filtered with syringe filter (0.45 µm) and analyzed by UV-VIS spectrophotometer (Shimadzu UV 1800) at 241 nm. Results are shown in table No.5

Fourier transforms Infrared spectroscopy (FTIR):

To study the interaction between drug and polymers used in the preparation of solid dispersion. FTIR spectrum of pure Carvedilol, polymer and physical mixtures were recorded. The drug and polymers separately and in combination with each other were mixed with KBr for determination of spectrum. The range selected was from 600 cm-1 to 3800cm-1(Figure No 4-8)

RESULT AND DISCUSSSION

Flow properties

Solid dispersion prepared by kneading method was evaluated for their flow properties such as Bulk density, Tapped density, Compressibility index, Hausner's ratio, and angle of repose. The Bulk density of solid dispersion was found in the ranges of 0.782 gm/ml to 0.087 gm/ml. The Tapped density of solid dispersion was found to be in the ranges of 0.939 ± 0.052 gm/ml to 1.073 ± 0.06 gm/ml. The Compressibility index of solid dispersion was found to be 17.61 ± 6.51 % to 24.98 ± 5.95% it indicates fair to passable flow properties The Hausner's ratio for solid dispersion was found in the ranges of 1.19 ± 0.04 to The Angle of repose for solid dispersion was found in the ranges of 37.31 and 39.11. Results are shown in table No. 1

Solubility studies

The solubility of Carvedilol in water was found to be approximately 18 mg/ml. significantly

increasing in solubility was obtained for all dispersions of Carvedilol with hydrophilic polymers. Solubility of all solid dispersion can be increased as compared to pure drug by solid dispersion. Solubility of PVP K90 and poloxamer 188 at 1:1, 1: 2, 1:4 ratios gives 24.50, 30.14, 50.14, 41.50, 51.26, 61.12 mg/ml respectively. Maximum solubility was observed in solid dispersion of Carvedilol and poloxamer 188 at 1:4 ratios (B4), considered as optimized solid dispersion of drug. Increase in solubility may be due to hydrophilic nature of the polymers, decreased agglomeration and aggregation of drug particles, particle size reduction to molecular size. The increase in solubility with increasing poloxamer concentration indicates the solvent properties of the poloxamer 188 for the drug. Poloxamer 188 causes decrease interfacial tension between the drug and dissolution medium. These results could be explained that reduction in crystallinity of the drug lead to decrease of the energy required for the dissolving process and also to a highly dispersed state of the drug. Results are shown in table No.3

Drug content

Solid dispersion prepared by kneading method was evaluated for drug content. The drug content of all dispersions was found to be in between 91 to 99 %. The drug content of different batches such as A1 is 92.44 %, A2 is 91.19%, A4 is 93.03%, B1 is 93.60%, B2 is 94.71% and B4 is 99.34 % drug content respectively. The optimized batch is B4 which shows high drug content as compared to other batches. Results are shown in table No.4

Dissolution study

The drug release profile for all formulations was shown in table. The dissolution rate of Carvedilol from various solid dispersions was studied in 0.1 N HCl. The dissolution rate of Carvedilol from all dispersions was significantly higher than that of Carvedilol. The drug release of PVP K90 and poloxamer 188 at 1:1, 1:2, and 1:4 ratio gives 80.177, 86.760, 91.932, 89.58, 94.753, and 99.935% respectively. The optimized batch is B4 which contain poloxamer 188 and Carvedilol at 1:4 ratios which give 99.925% drug release in 60 min as compared to PVP K90 which give only 91.932% drug release in 60 min. As we increase the concentration of polymer increases the dissolution rate of the drug. Results are shown in table No.5

The improvement of dissolution rate possibly caused by several factors such factors are.

- The strong hydrophilic character of poloxamer 188 which improves the water penetration and wettability of the Carvedilol.

- Absence of crystal corresponds to lower energy required for dissolution.

Fourier transforms Infrared spectroscopy

FTIR of pure Carvedilol shows characteristics bands belonging to Carbazol moiety at 1100, 1500, 2900 Cm -1 corresponding to aromatic secondary C-N vibrations, C=C multiple bonds stretching, and C-H stretching of aromatic ring respectively. FTIR-spectra of drug and its physical mixture with polymers are exactly same, and there is no shift of peaks or disappearance of principle peaks or modification of the principle peaks indicating that there is no interaction between the drug and excipients. (Figure No. 4-8)

Table No.1: codes for prepared solid dispersions of Carvedilol with carriers

Sr. No.	Solid dispersion system	Codes for dispersion
1	Carvedilol	A
2	Carvedilol+ PVP K90	A1
3	Carvedilol+ PVP K90	A2
4	Carvedilol+ PVP K90	A4
5	Carvedilol + poloxamer 188	B1
6	Carvedilol + poloxamer 188	B2
7	Carvedilol + poloxamer 188	B4

Table No.2 flow properties of solid dispersion

Formulation Code	Bulk density (gm/ml)	Tapped density (gm/ml)	Compressibility Index (CI) (%)	Hausner's ratio (HR)	Angle of repose (θ)
A1	0.087±0.03	1.073 ± 0.06	20.09 ± 4.22	1.19 ± 0.04	37.31 ± 2.194
A2	0.81 ± 0.03	1.00 ± 0.09	17.61 ± 6.51	1.21 ± 0.10	37.10 ± 4.60
A4	0.81 ± 0.06	1.09 ± 0.171	24.67 ± 5.95	1.32 ± 0.10	38.53 ± 1.005
B1	0.768 ±0.04	0.939 ± 0.052	18.95 ±3.15	1.26 ± 0.01	38.25 ± 2.494
B2	0.782 ± 0.112	0.950 ± 0.14	24.98 ± 5.38	1.30 ± 0.03	37.22 ± 0.629
B4	0.83 ± 0.03	1.09 ± 0.03	23.48 ± 1.64	1.30 ± 0.03	39.11 ± 1.005

Table No.3: Solubility study of Carvedilol solid dispersion

Sr. No.	Formulation code	Drug : carrier ratio	Solubility mg/ml
1	A	Pure drug	18
2	A1	Carvedilol+ PVP K90(1:1)	24.50
3	A2	Carvedilol+ PVP K90(1:2)	30.14
4	A4	Carvedilol+ PVP K90(1:4)	50.14
5	B1	Carvedilol + poloxamer 188(1:1)	41.50
6	B2	Carvedilol + poloxamer 188 (1:2)	51.26
7	B4	Carvedilol + poloxamer 188 (1:4)	61.12

Table No.4: Drug content of solid dispersion

Sr. No.	Formulation code	Drug : carrier ratio	% Drug content
1	A1	Carvedilol+ PVP K90(1:1)	92.44
2	A2	Carvedilol+ PVP K90(1:2)	91.19
3	A4	Carvedilol+ PVP K90(1:4)	93.03
4	B1	Carvedilol + poloxamer 188(1:1)	93.60
5	B2	Carvedilol + poloxamer 188 (1:2)	94.71
6	B4	Carvedilol + poloxamer 188 (1:4)	99.34

Table No.5: % Drug release from solid dispersion

Sr. No.	Time(min)	A1	A2	A4	B1	B2	B4
1	5	11.016	28.139	30.096	20.101	24.714	28.668
2	10	17.766	33.334	35.767	27..10	33.821	35.280
3	15	25.891	38.953	41.372	33.148	43.791	43.791
4	20	31.037	45.469	48.356	42.102	50.761	52.204
5	30	40.907	57.650	57.650	50.953	60.041	62.433
6	40	58.273	68.737	70.640	63.981	68.262	74.921
7	50	70.236	76.857	82.069	76.857	80.640	87.261
8	60	80.177	86.760	91.932	89.581	94.753	99.925

Table No.6: values of absorbance

Concentration (µg/ml)	Absorbance
0	0
2	0.161
4	0.312
6	0.45
8	0.605
10	0.739
12	0.890
14	0.999

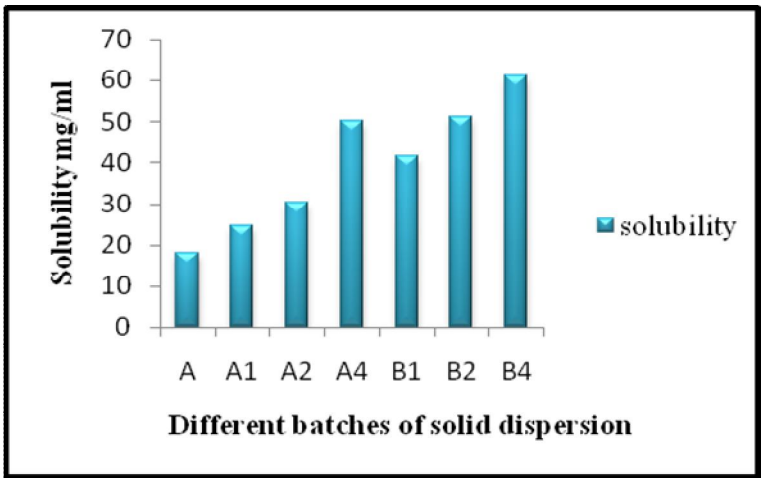

Fig No: 1 Solubility study of different batches of solid dispersion

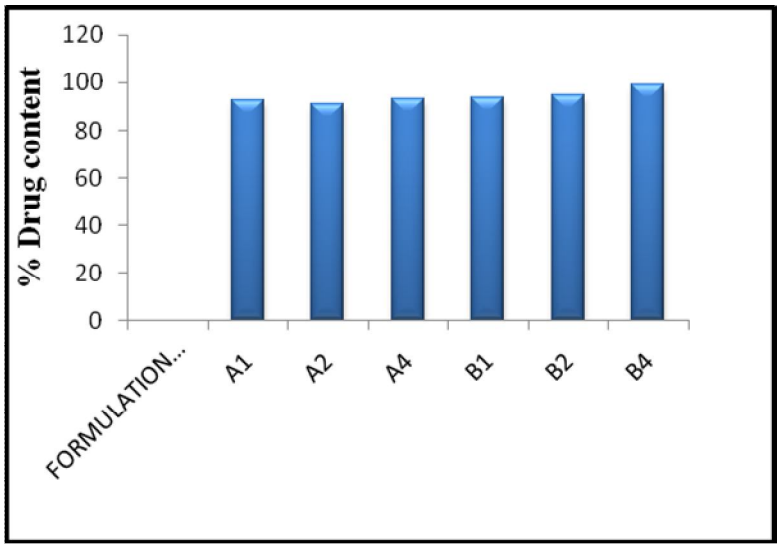

Fig No.2 Drug content of different batches of solid dispersion

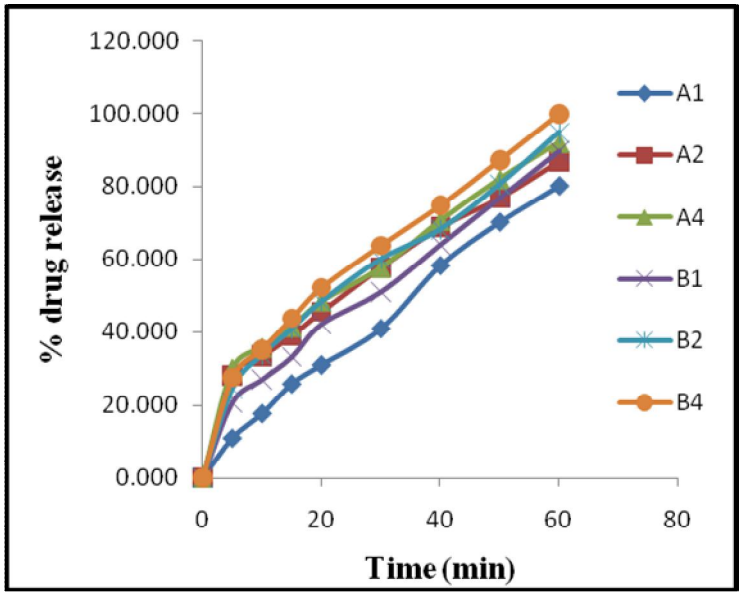

Fig No. 3: % Drug release from different batches of solid dispersion

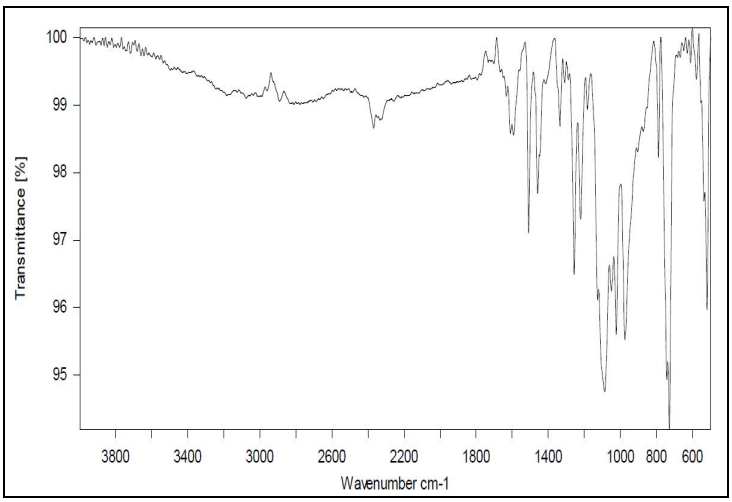

Fig No.4: FTIR Spectra of Carvedilol

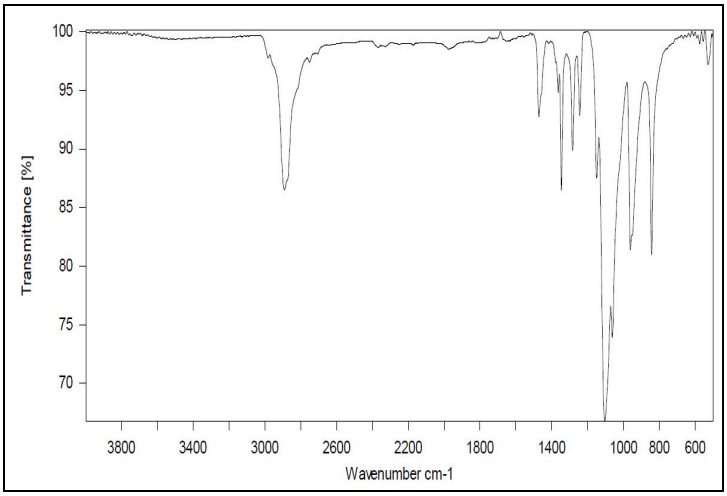

Fig No.5: FTIR Spectra of poloxamer 188

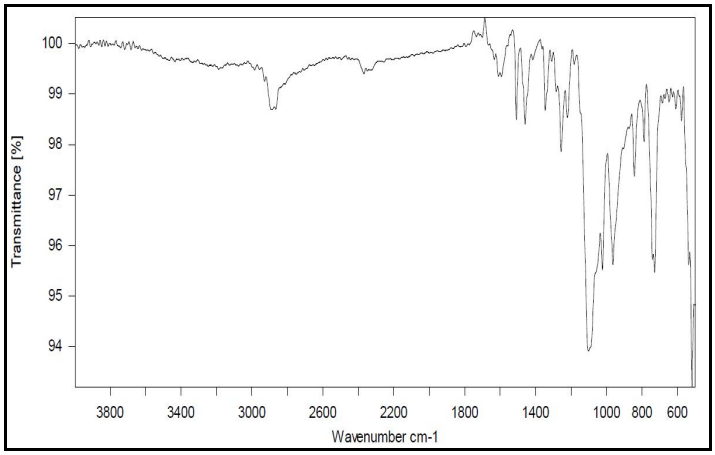

Fig No.6: IR spectra of physical mixture of Carvedilol and poloxamer 188

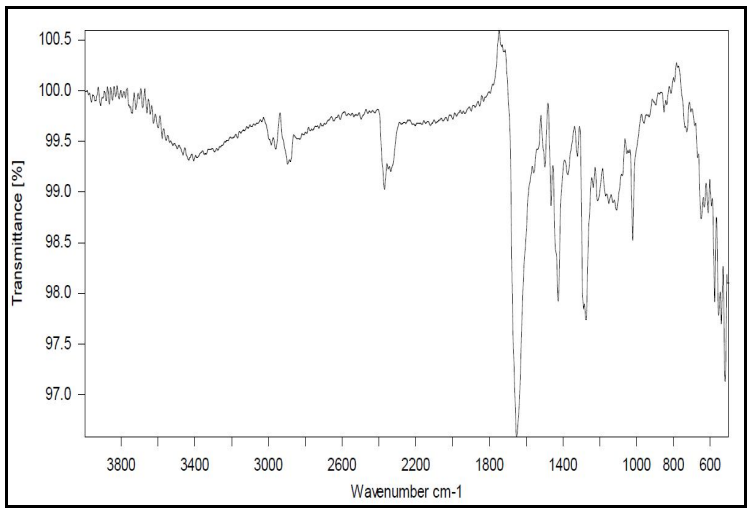

Fig No.7: IR spectra of PVP K90

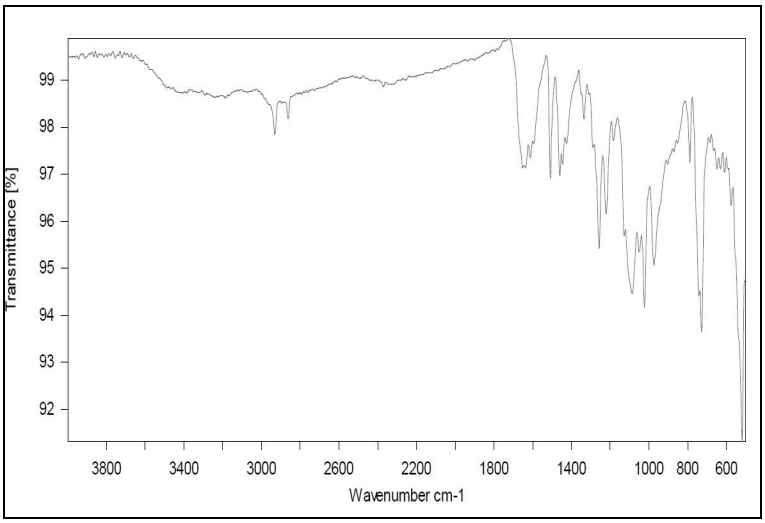

Fig No.8: IR spectra of physical mixture of Carvedilol and PVP K90

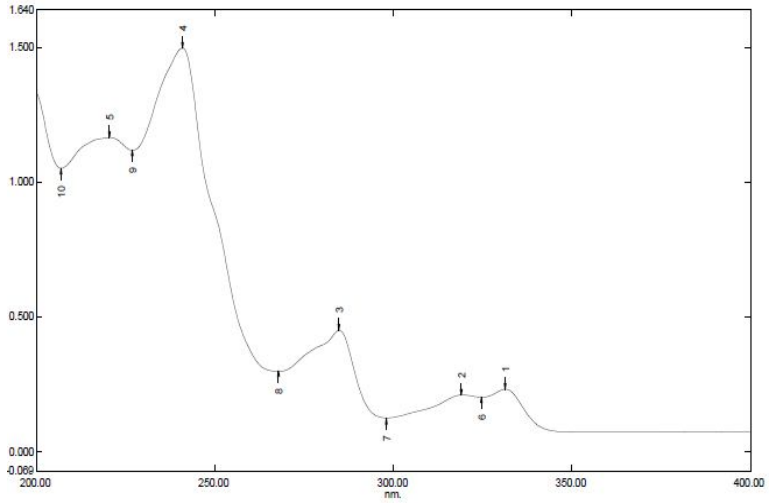

Fig No.9: λ max of Carvedilol in 0.1 N HCl

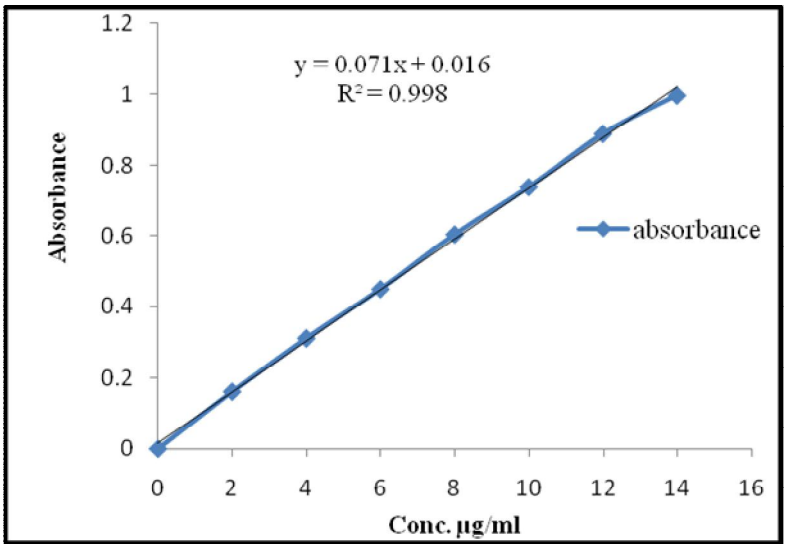

Fig No.10: Standard Calibration curve of Carvedilol

CONCLUSION

The solubility and dissolution profile of Carvedilol was significantly improved by preparing solid dispersion with water soluble carrier like PVP K90 and poloxamer 188 by kneading method. These solid dispersions were evaluated for solubility study, drug content and dissolution study. The techniques explored are relatively easy, simple, quick, and inexpensive. The IR study showed no signs of interactions of the drug with the carrier. Further, it may be assumed that the solubility and dissolution rate can be increased due to the conversion of crystalline matter into amorphous powder. Hence we can conclude that solid dispersion of Carvedilol by using the water soluble carrier poloxamer 188 in the ratio1:4 prepared by kneading method provide best release of drug (99.925% drug release in 60 min.)

among all the formulations and this ratio can be used to enhance the solubility and dissolution rate of poorly water soluble drug Carvedilol.

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