www.ThePharmaJournal.com

The Pharma Innovation

Kavita Bahmani
Assistant Professor
Department of Pharmaceutical
Sciences, Chaudhary Bansi Lal
Universit, Bhiwani, Haryana,
India

Yashpaul Singla
Department of Pharmaceutical
Sciences G.J.U.S & T, Hisar,
Haryana, India

Enhanced solubility of antihypertensive drug using hydrophilic carrier-based potent solid dispersion systems

Kavita Bahmani, Yashpaul Singla

Abstract
Oral bioavailability enhancement of drug having poor water solubility is considered as a very hard task in the formulation development of such drugs. The development of solid dispersions helps to enhance bioavailability of poorly water soluble drugs to overcome the limitations of various approaches such as salt formation, solubilization by co-solvents, and particle size reduction. Studies revealed that drugs in solid dispersion need not necessarily exist in the micronized state. Carvedilol's β-adrernergic receptor blocking ability decreases the heart rate, myocardial contractility and myocardial oxygen demand. Carvedilol and its metabolites also prevent OH⁻ radical induced decrease in sarcoplasmic reticulum Ca-ATPase activity. Therefore, carvedilol and its metabolites may be beneficial in the chronic heart failure by preventing free radical damage. Carvedilol belongs to BCS class-II drug having poor water solubility. For the improvement of solubility solid dispersions of carvedilol were prepared using fusion method. Various concentrations of polymers like mannitol and PVPK-30 were used for the preparation o solid dispersions.

Keywords: Solid dispersions; bioavailability; carvedilol (CRL); mannitol; PVP-K30

Introduction
The therapeutic effectiveness of a drug depends upon the ability of the dosage forms to deliver the medicament to its site of action at a rate and amount sufficient to elicit the desired pharmacologic response. The formulation of poorly water soluble drugs has always been a challenging problem faced by pharmaceutical scientists and it is expected to increase because approximately 40% or more of the new chemical entities being generated through drug discovery programmers are poorly water soluble. Low solubility, low dissolution rate, poor intestinal permeability, intestinal cellular efflux, chemical instability in the gastrointestinal tract, mucin binding, rapid metabolism, absorption via a low capacity active transporter, and limited absorption due to a narrow transit period must be considered as contributing factors for poor bioavailability.

The BCS is scientific framework for classifying drug substances based on their aqueous solubility and intestinal permeability. When combined with the dissolution of the drug product, the BCS takes into account three major factors that govern the rate and extent of drug absorption from solid oral dosage forms: dissolution, solubility and intestinal permeability. According to the BCS drug substances are classified as follows:
Class I: High Solubility – High Permeability
Class II: Low Solubility – High Permeability
Class III: High Solubility – Low Permeability
Class IV: Low Solubility – Low Permeability
Solid dispersion technology is the science of dispersing one or more active ingredients in an inert matrix in the solid stage to achieve an increased dissolution rate or sustained release of drug, altered solid state properties and improved stability. The fusion process is technically less difficult method of preparing dispersions provided the drug and carrier are miscible in the molten state.

Materials and Methods
Materials
Carvedilol was kindly supplied by M/s Shodhana Labs Ltd. Hyderbad, India as a gift sample. Mannitol, PVP K-30, PEG- 6000 and ethanol etc. were used as ingredients for the formulation of solid dispersion of carvedilol.

**Correspondence
Kavita Bahmani**
Assistant Professor
Department of Pharmaceutical
Sciences, Chaudhary Bansi Lal
Universit, Bhiwani, Haryana,
India

Methods

Characterization of Drug
The procured sample of carvedilol was characterized in terms of its physical description, organoleptic properties, melting point and solubility in various solvents.

Melting Point Determination
A small quantity of carvedilol was filled in the capillary tube sealed at one end and kept it in melting point apparatus. The melting point was recorded and compared with literature value of carvedilol.

Solubility Studies
The solubility of carvedilol was checked in distilled water and 0.1 N HCL at room temperature for 24 h using rotary shaker. Solubility of the drug was determined by saturation method. Using slope of drug the solvent concentration of drug in the solution was determined. From this concentration, amount dissolved in the solvent i.e. solubility was determined.

Studies on Interference of Carries(S) on Drug UV Spectrum
Carvedilol (12.5 mg) was dissolved in methanol and volume was made upto 100 mL with 0.1 N HCL. After suitable dilutions, the U.V. spectrum of drug was obtained. In similar way, U.V. spectra of carrier(s) *viz.* Mannitol and PVP K- 30 were obtained in the wavelength region 200 - 400 nm at their respective maximum amounts employed in the study.

Preparation of Physical Mixtures
In order to prepare a physical mixture the drug, carrier(s) were passed individually through sieve # 100. Various physical mixtures were prepared by homogeneously mixing the drug and the carrier(s) for 15 min. and subsequently filling into empty hard gelatin capsules.

Preparation of Solid Dispersions
All the solid dispersions of carvedilol were prepared using water soluble carriers *viz.* mannitol and PVPK -30 in various ratios by fusion method. In this method, the drug was incorporated into previously molten carrier(s), homogenously blended and subsequently flashed cooled in an ice-bath. The resulting solid dispersions were stored for 24 hrs in a dessicator to congeal. Finally, dispersions were passed through sieve $\pm$ 100 and filled into empty hard gelatin capsules

In-vitro - Dissolution Studies
The *In-vitro* dissolution studies on pure drug (12.5mg) and physical mixtures and solid dispersion formulations of carvedilol were carried out in triplicate, employing USP XXIII paddle (Apparatus 2) using 900 mL 0.1 N HCL, as the dissolution medium at 100 rpm and 37±0.5˚C. An aliquots sample (10 mL) was periodically withdrawn at suitable time intervals and volume replaced with equivalent amount of dissolution medium. The samples were analyzed on spectrophometer at 241.2 nm using UV-visible spectrophotometer.

Data Analysis
The data obtained from *in-vitro* dissolution were analyzed using PCP Disso V3 software. The software is in built provision for applying the correction factor for volume and drug losses during sampling, calculating the values of amount of drug dissolved, percent release, rate of drug release at varied time. The graph was drawn using MS-EXCEL.

Characterization of Physical Mixture and Solid Dispersion of Carvedilol

Powder X-Ray Diffraction (PXRD)
PXRD patterns ware recorded using high power powder x-ray diffracto meter with Cu as target filters having a voltage/current of 40 KV/40 mA at a scan speed of 4 degree/min. The samples were analyzed at angle range of 2 to 45 step time was 0.5 second and time of acquisition was 1 hour.

Differential Scanning Calorimetry (DSC)
DSC analysis of the drug, carriers, one of the selected formulation and its physical mixture were carried out by heating the samples from 25 ℃ to 250 ℃ at a rate of 10 ℃ per minute.

Fourier Transforms Infrared Spectroscopy (FTIR)
FTIR spectroscopy was performed on I.R. spectrophotometer. Pellets of the drug samples in KBr were prepared on KBr press. The spectra were scanned over a wave number range of 4000 to 400 cm^{-1}.

Scanning Electron Microscopy (SEM)
Sample were coated with thin gold- palladium layer using a sputter coater unit and the surface topography was analyzed with (JCM-6100, Scanning electron microscope, Japan) operated at acceleration voltage of 15 Kv. The samples were mounted onto stubs using double sided adhesive tape. The samples were then coated with gold palladium alloy (150- 200 A°) using fine coat ion sputter (Jeol, fine coat ion sputter JFC-1100). The samples were subsequently examined under a scanning electron microscope.

Results and Discussion

Melting Point Determination
The melting point of carvedilol was observed to be 115.33 ˚C which is in close agreement of reported values i.e. 114 ˚- 115 ˚C.

Table 1: Melting Point of Carvedilol

S. No.	Melting Point (°C)	Mean Value ± S.D.(˚C)
1	119	
2	117	115.33 ± 2.334
3	110	

Studies on Interferences of Carrier(S) on Drug UV Spectrum
No interaction of the carrier (s) *viz.* Mannitol and PVP K-30 was seen on the UV spectrum of carvedilol

Solubility Studies
Solubility studies were carried out as an attempt to find out whether the medium 0.1 N HCL was able to maintain sink condition during the dissolution studies or not. The solubility of pure drug in distilled water and 0.1 N HCL is depicted in Table given below. The result indicated that the solubility of carvedilol in 0.1 N HCL was 1.062 mg/ml. Since a total dose of 12.5 mg of drug was planned to be subjected for dissolution using 900 mL of medium, the equilibrium solubility was much higher than the maximum concentration of the drug any time during dissolution process. Therefore, 0.1 N HCL was chosen as the dissolution medium because sufficient amount of drug can dissolve in it, necessary to maintain sink conditions.

Table 2: Solubility of carvedilol in various solvents

S. No.	Solvents	Solubility (mg/mL)
1	Distilled water	0.323 mg/mL
2	0.1 N HCL	1.062 mg/mL

In-vitro Dissolution Studies

Tables given below enlist the dissolution performance of various solid dispersions prepared using mannitol and PVP K-30 as carriers and their corresponding release profiles are shown in figures below.

Table 3: Values of Percent Drug Released at Varied Times for Solid Dispersions of Carvedilol and Mannitol (N=3)

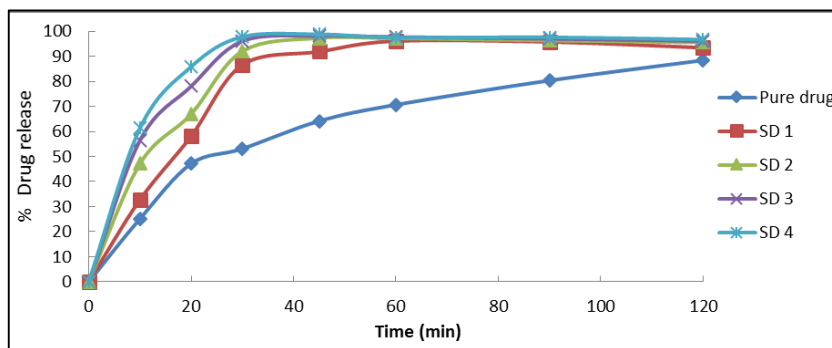| Time (min)	Mean Percent Drug Dissolution ± S.D				
	Pure Drug	CRL: Mannitol 1:1 (SD1)	CRL: Mannitol 1:2 (SD 2)	CRL: Mannitol 1:3 (SD 3)	CRL: Mannitol 1:5 (SD 4)
0	0	0	0	0	0
10	25.153±1.67	32.753±1.42	47.1±1.86	56.46±1.67	61.31±2.42
20	47.121±2.3	58.108±1.62	66.92±2.13	78.04±2.38	85.85±2.67
30	53.110±.68	86.106±0.24	92.03±0.11	96.07±0.19	97.8±0.28
45	64.162±.10	91.13±0.40	97.31±0.18	98.16±0.21	98.79±0.41
60	70.652±.28	96.35±0.27	97.18±0.24	97.73±0.12	97.5±0.28
90	80.352±.26	95.74±0.18	96.31±0.34	97.01±0.09	97.6±0.18
120	88.431±.31	93.41±0.14	95.56±0.21	96.13±0.14	96.69±0.25

Fig 1: Plot between % Drug Released and Time for Various Carvedilol-Mannitol Solid Dispersions

Table 4: Values of Percent Drug Released at Varied Times for Solid Dispersions of Carvedilol and PVP K-30 (N=3)

| Time (min)	Mean Percent Drug Dissolution ± S.D				
	Pure Drug	CRL:PVP K-30 1:1 (SD 5)	CRL: PVP K-30 1:2 (SD 6)	CRL: PVP K-30 1:3 (SD 7)	CRL: PVP K-30 1:5 (SD 8)
0	0	0	0	0	0
10	25.153±0.19	30.153±.11	37.42±.68	45.13±.12	52.93±0.01
20	47.121±0.11	51.121±.40	60.36±.10	65.83±.18	69.42±0.03
30	53.110±0.25	57.110±.21	61.280±.28	72.62±1.34	77.19±0.10
45	64.162±0.18	66.162±.18	71.18±.31	79.38±.169	81.36±0.06
60	70.652±0.28	77.652±.11	81.83±.26	87.12±1.68	88.12±0.92
90	80.352±0.41	83.352±.10	88.16±.18	93.37±1.31	94.34±0.29
120	88.431±0.28	90.431±.34	92.103±1.20	95.39±0.62	96.68±0.31
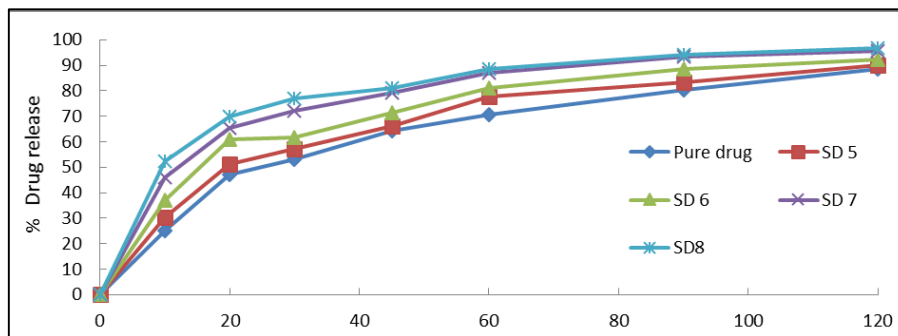
Fig 2: Plot between % Drug Released and Time for Carvedilol – PVP K-30 Solid Dispersions.

On studying *in vitro* release study the mannitol dispersions had profound influence on the release profile of carvedilol. The results, however, were almost identical at or above 1:2 Drugs: Mannitol ratios. There was also improved release performance of PVP K-30 solid dispersions in comparison to pure drug. The effect of low concentration of PVP K-30 was milder. The result of higher concentration (1:3 and 1:5) of PVP K-30 showed better and almost identical release performance throughout the dissolution profile.

Physical mixtures

During initials studies the physical mixtures of carvedilol (CRL) with two chosen carries (i.e., Mannitol and PVP K-30) were also prepared by taking drug: carrier ratio of 1:1, 1:2 1:3 and 1:5 respectively. Tables given below enlist the dissolution parameters of these physical mixtures and also figures given below showed their dissolution profiles.

Table 5: Values of percent drug released at varied times for physical mixtures of Carvedilol and Mannitol (n=3)

Time (min)	Mean Percent Drug Dissolution ± S.D				
	Pure Drug	CRL: Mannitol 1:1(PM1)	CRL: Mannitol 1:2(PM2)	CRL: Mannitol 1:3(PM3)	CRL: Mannitol 1:5(PM4)
0	0	0	0	0	0
10	25.153±0.41	27.753±3.53	29.1±2.10	32.46±1.08	38.31±1.07
20	47.121±0.16	51.108±3.41	54.92±1.19	57.04±1.87	62.85±1.32
30	53.110±0.34	56.56±0.07	60.03±1.68	63.07±1.67	67.8±0.13
45	64.162±0.14	65.89±1.32	68.31±2.67	71.16±1.82	79.79±0.12
60	70.652±0.21	74.08±2.18	78.18±1.23	82.73±0.67	84.5±0.16
90	80.352±0.11	83.74±0.98	87.31±1.44	89.01±0.03	91.6±0.13
120	88.431±0.12	90.41±0.68	92.56±0.32	94.13±0.66	95.69±1.67
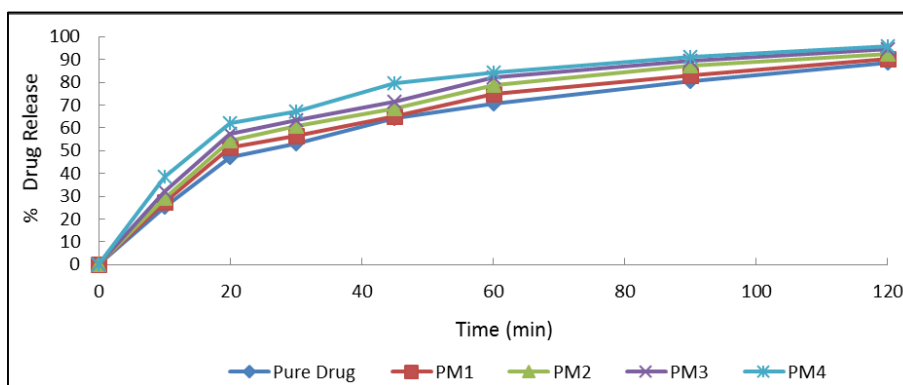
Fig 3: Plot between % Drug Released and Time for Various CRL-Mannitol Physical Mixtures.

Table 6: Values of Percent Drug Released At Varied Times for Physical Mixtures of Carvedilol and PVP K-30 (**n=3**)

| Time (min)	Mean Percent Drug Dissolution ± S.D				
	Pure Drug	CRL:PVP K-30 1:1(PM5)	CRL: PVP K-30 1:2 (PM6)	CRL: PVP K -30 1:3 (PM7)	CRL: PVP K-30 1:5 (PM8)
0	0	0	0	0	0
10	25.153±0.67	26.208±0.86	28.431±0.12	29.36±1.42	32.29±0.10
20	47.121±0.68	49.13±0.82	51.513±1.23	53.131±1.48	62.103±0.21
30	53.110±1.23	56.16±0.13	58.18±1.68	59.321±1.92	68.118±0.13
45	64.162±0.38	67.103±0.67	68.213±0.62	69.123±2.61	76.129±0.12
60	70.652±1.32	71.236±0.92	73.103±1.36	77.113±3.42	82.103±0.21
90	80.352±1.64	84.85±0.10	87.721±2.21	90.81±4.13	92.117±0.13
120	88.431±1.32	89.03±0.34	91.136±2.36	92.108±3.10	94.121±1.63
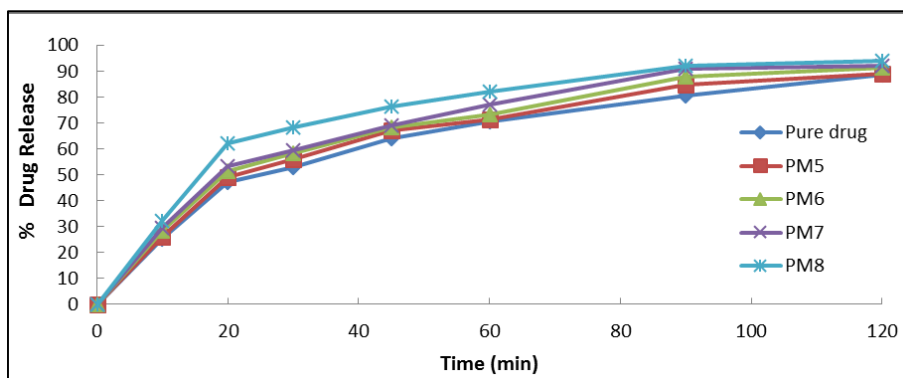
Fig.4: Plot between % Drug Released and Time for Carvedilol-PVP K-30 Physical Mixtures

As is indicated by the dissolution study mannitol and carvedilol physical mixtures had only marginally better release performance than that of pure drug. CRL and PVP K-30 mixtures also exhibit marginally better release than that of pure carvedilol. Again from the results it was observed that physical mixtures of both carvedilol –Mannitol and carvedilol – PVP K-30 exhibits better release performance by increasing the drug – carrier ratios.

However, improvement in release performance was not significantly better than that of the pure drug. This all indicates that the improvement in the dissolution performance of carvedilol by Mannitol or PVP K-30 cannot attribute to

simple synergistic effect of Mannitol or PVP K-30, when used as physical mixtures. Nonetheless, the release performance of the corresponding solid dispersion was distinctly superior to that of the physical mixtures.

Characterization of Solid Dispersion
Differential Scanning Calorimetery (DSC) Study

Table given below depicts various DSC characteristics of pure carvedilol, mannitol, PVP K-30; selected solid dispersion formulation prepared using mannitol or PVP K-30 and their corresponding physical mixtures. DSC curve for pure carvedilol shows a single fusion endotherm, representing the melting point at 116.77 ℃ and exhibits the normalized value of 127.4 Jg⁻

Table 7: Characteristics of Differential Scanning Calorimetry of Carvedilol, Mannitol PVP K-30, Solid Dispersion Formulations and their Corresponding Physical Mixtures.

| S. No.	Formulation	Normalized Value (Jg⁻¹)	Onset of Endotherm (Degrees)	Peak of Endotherm (Degree)
1.	Carvedilol	127.4	113.27	116.77
2.	PVP K-30	150.5	137.13	143.66
3.	Mannitol Peak 1	36.82	96.48	101.89
	Mannitol Peak 2	51.11	151.30	168.67
4.	Physical mixture with PVP K-30	819.9	143.98	146.99
5.	Physical mixture with Mannitol	812.6	142.99	146.99
6.	Solid dispersion with PVP K-30	148.6	113.74	117.87
7.	Solid dispersion with Mannitol	246.4	137.80	135.35
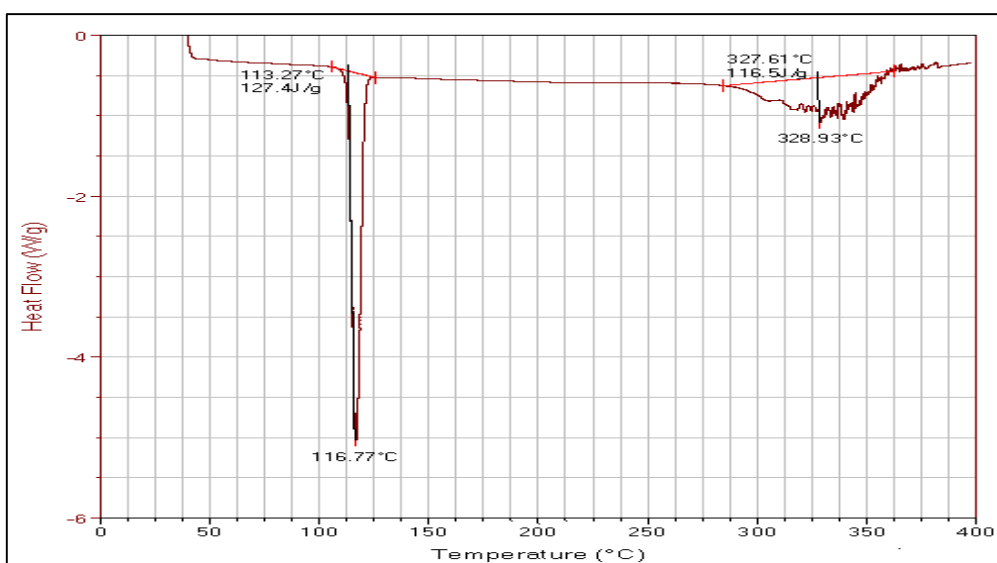
Fig 5: DSC Thermogram of Carvedilol
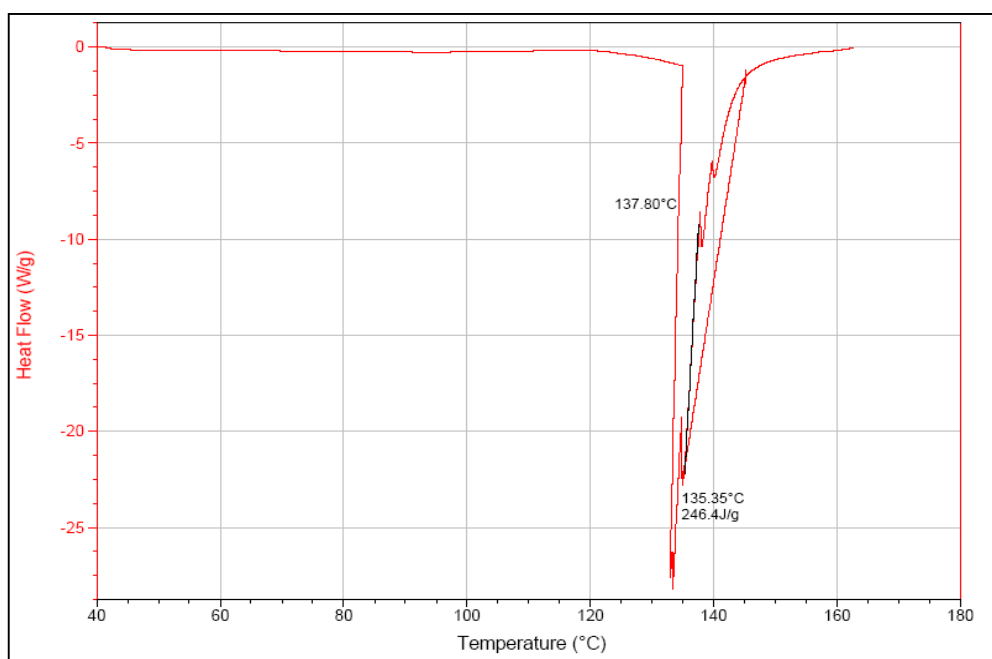

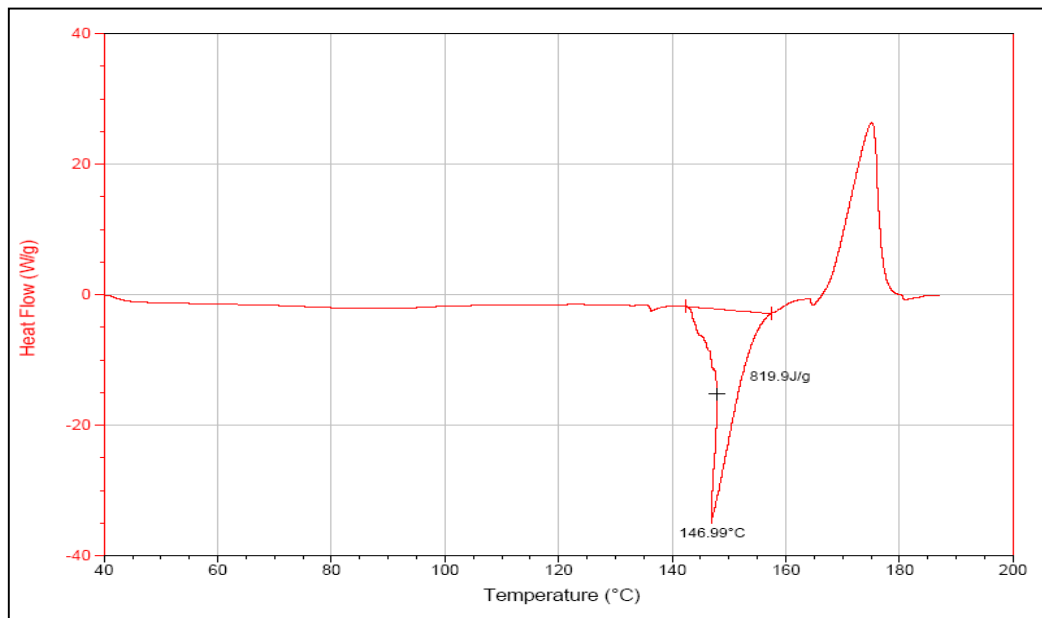**Fig. 6:** DSC Thermogram of Solid Dispersion of Carvedilol with Mannitol

Fig 7: DSC Thermogram of Solid Dispersion of Carvedilol with PVP K-30

X-ray Diffraction Studies

The X-ray diffracto gram for the pure drug carvedilol is show in figure below, whereas its characteristic peaks at 2θ (in degrees) listed in table given below. On comparing the x-ray diffracto grams of the selected solid dispersions formulations with mannitol or PVP K-30 and their physical mixtures, it can be deciphered that the crystallinity of carvedilol is reduced drastically in the solid dispersions vis-à-vis their corresponding physical mixtures. Significant diminution in the number of peaks as well as in the corresponding amplitude of peaks is vividly discernable.

Table 8: Characteristics Peaks of Pure Carvedilol, Mannitol, PVP K-30, Solid Dispersion and their Corresponding Physical Mixture

| S. No.	Formulation	Characteristics Peak at 2 Θ (degrees)
1	Pure carvedilol	5.7, 8.1, 11.8, 12.9, 13.6, 14.7, 15.5, 16.9, 17.8, 19.1, 20.9, 21.6, 22.8, 23.5, 24.3, 25.3, 26.1, 27.5, 28.1, 29.3, 31.4, 32.4, 34.1, 36.6, 38.0, 41.8, 42.7, 43.5, 44.7, 46.6, 48.0
2	Pure Mannitol	10.5, 11.4, 14.5, 16.7, 20.5, 21.7, 23.4, 24.6, 25.9, 26.6, 28.3, 29.5, 30.5, 31.8, 32.7, 33.6, 34.2, 35.9, 36.5, 37.7, 38.7, 40.2, 41.0, 42.9, 44.1, 45.6, 47.9
3	Pure PVP K-30	43.45.7
4	Physical mixture of carvedilol with Mannitol	5.8, 10.4, 11.8, 13.6, 14.8, 15.2, 16.8, 17.5, 18.7, 19.6, 20.5, 21.6, 22.8, 23.4, 24.6, 25.9, 26.5, 27.5, 28.3, 29.5, 30.5, 31.7, 32.6, 33.6, 34.8, 36.0, 38.7, 40.1, 41.7, 42.8, 43.3, 44.0, 45.5, 47.8
5	Physical mixture of carvedilol with PVP K-30	5.8, 11.8, 12.9, 13.6, 14.8, 15.1, 16.4, 16.8, 17.4, 18.4, 19.2, 20.2, 21.4, 22.8, 23.5, 24.2, 25.2, 26.1, 27.5, 28.1, 29.4, 31.5, 34.2, 38.0, 41.8, 43.5
6	Solid dispersion with Mannitol	9.6, 10.9, 13.6, 14.5, 17.2, 18.6, 20.3, 22.0, 25.8, 27.5, 28.4, 30.3, 31.3, 31.4, 36.1, 38.1, 39.5, 40.7, 41.4, 43.8, 44.8, 47.4, 48.2, 49.1
7	Solid dispersion with PVP K-30	11.2, 20.8
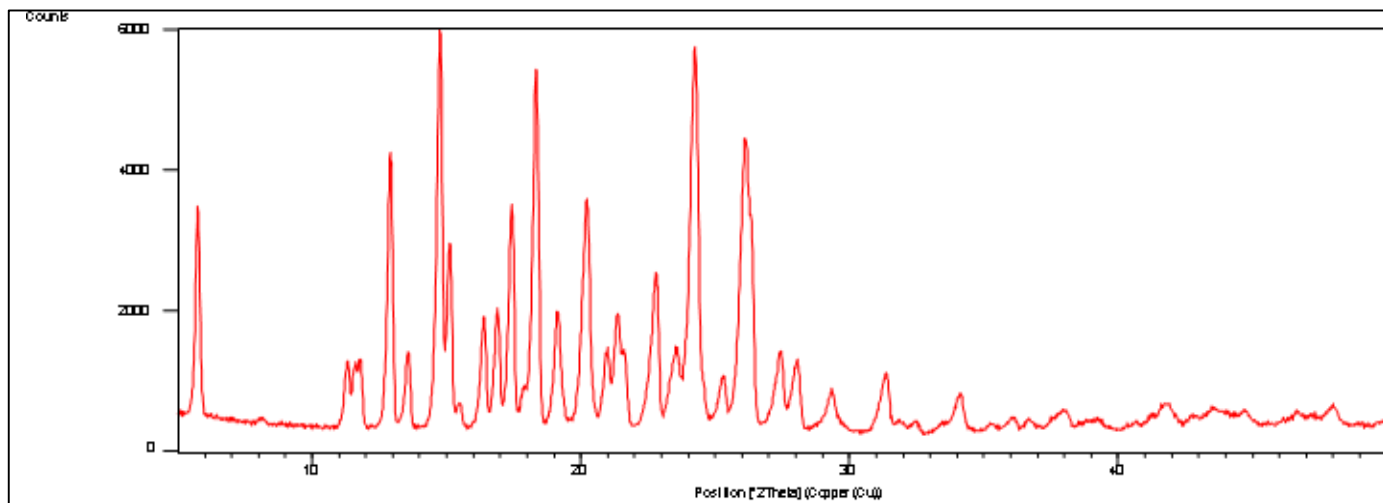
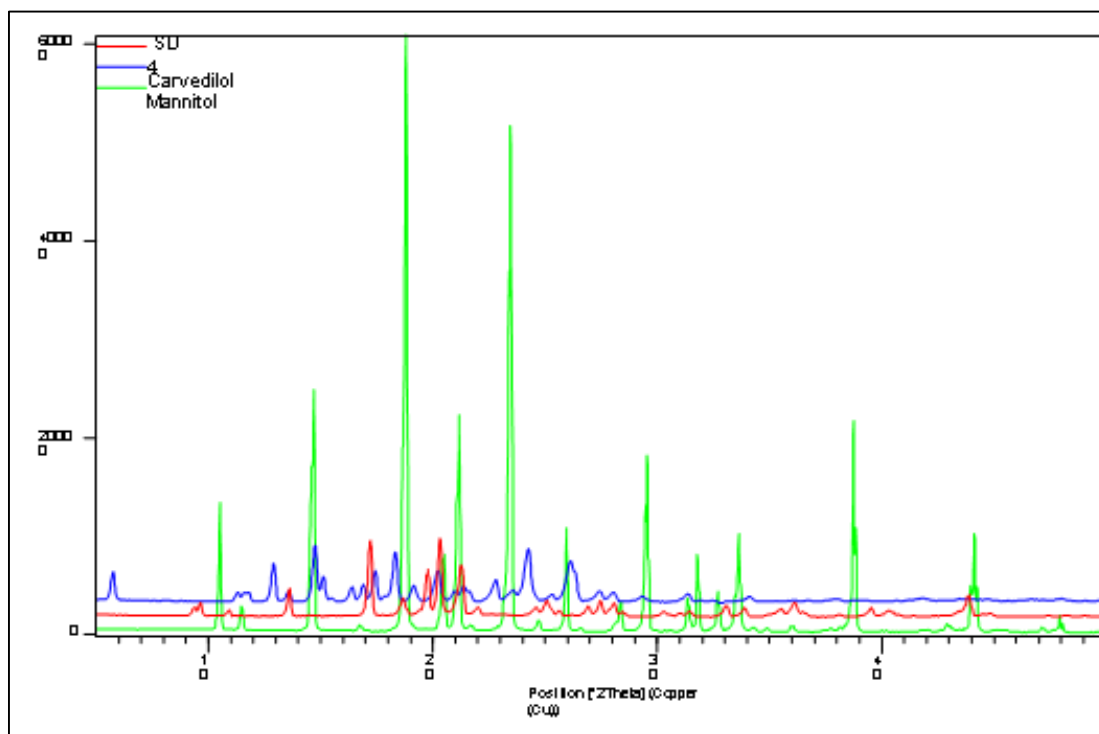**Fig 8:** XRD Pattern of Carvedilol

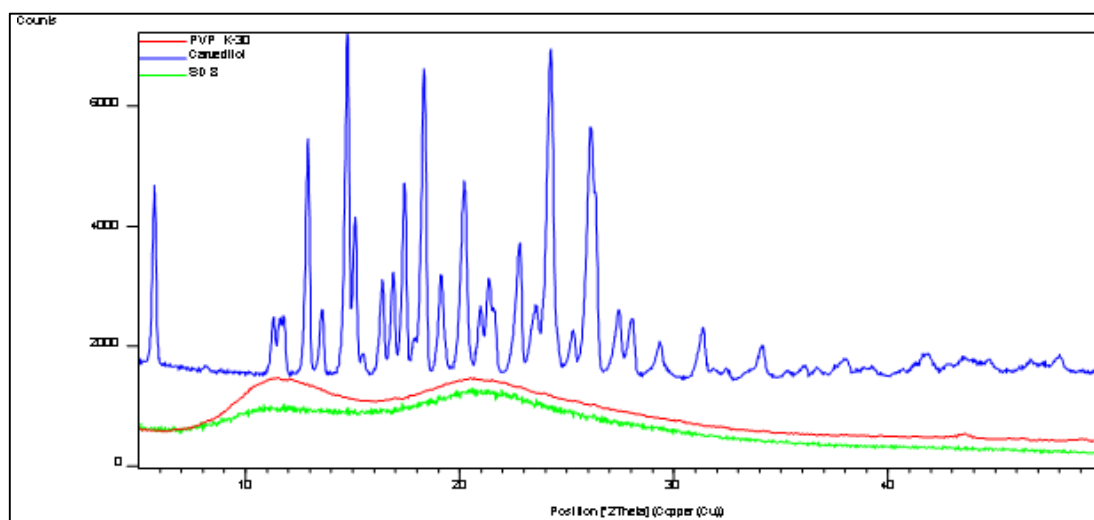**Fig 9:** XRD Pattern of Solid Dispersion of Carvedilol (CRL) With Mannitol

Fig 10: XRD Pattern of Solid Dispersion of Carvedilol with PVP K-30

FT –IR studies

In the IR spectra of carvedilol, absorption was observed at 3345.17 cm⁻¹ due to hydroxyl (-OH) and amine (-NH) stretching. Peaks at 2925.20 cm⁻¹, 1215.17 cm⁻¹ and 1017.0 cm⁻¹ are due to C-H starching, alkyl aryl ether stretching and bending vibrations respectively. Analysis of IR spectra of pure mannitol showed sharp peak at 3400 cm⁻¹ that is characteristics of O-H stretching vibrations and another set of sharp peaks were observed between 3000 cm⁻¹ - 2800 cm⁻¹, characteristics of C-H stretching vibrations. In the IR spectra of selected solid dispersion and its corresponding physical mixture (fig.34, 36), the characteristics absorption bands of pure carvedilol are distinctly appearing, as in both the cases i.e., N-H stretching in the carvedilol is distinctly appearing in the solid dispersion as well as in the physical mixture of carvedilol with mannitol. Both the spectra are more or less similar to each other. Hence, IR spectra did not indicate any kind of chemical interaction between the drug and the mannitol, in the solid dispersion formulation as well as physical mixture of the carvedilol. Analysis of IR spectra of the solid dispersions of carvedilol with PVP K-30 showed slight shift is the absorption values. It exhibited peaks due to -OHstr. and -NHstr. at 3436.32 cm⁻¹ while peak due to C-Hstr, alkyl ether stretching and bending appeared at 1215.93 cm⁻¹ and 1012.91 cm⁻¹ respectively. The above data indicated very week interactions between carvedilol and PVP K-30 solid dispersion. In case of physical mixture of carvedilol with PVP K-30, the change was observed in the range 2700 cm⁻¹ -3000 cm⁻¹, which were interpreted as -C-H stretching vibrations of the aromatic ring. Difference were also found in $\diagup C=C\diagdown$ (of the aromatic ring) vibration region (1450 cm⁻¹-1600 cm⁻¹). The absorption peaks due to alkyl aryl ether stretching and bending appeared at 1209.08 cm⁻¹ and 1025 cm⁻¹ respectively. The change in the intensity and shape of these bonds showed considerable interaction between carvedilol and PVP K-30.
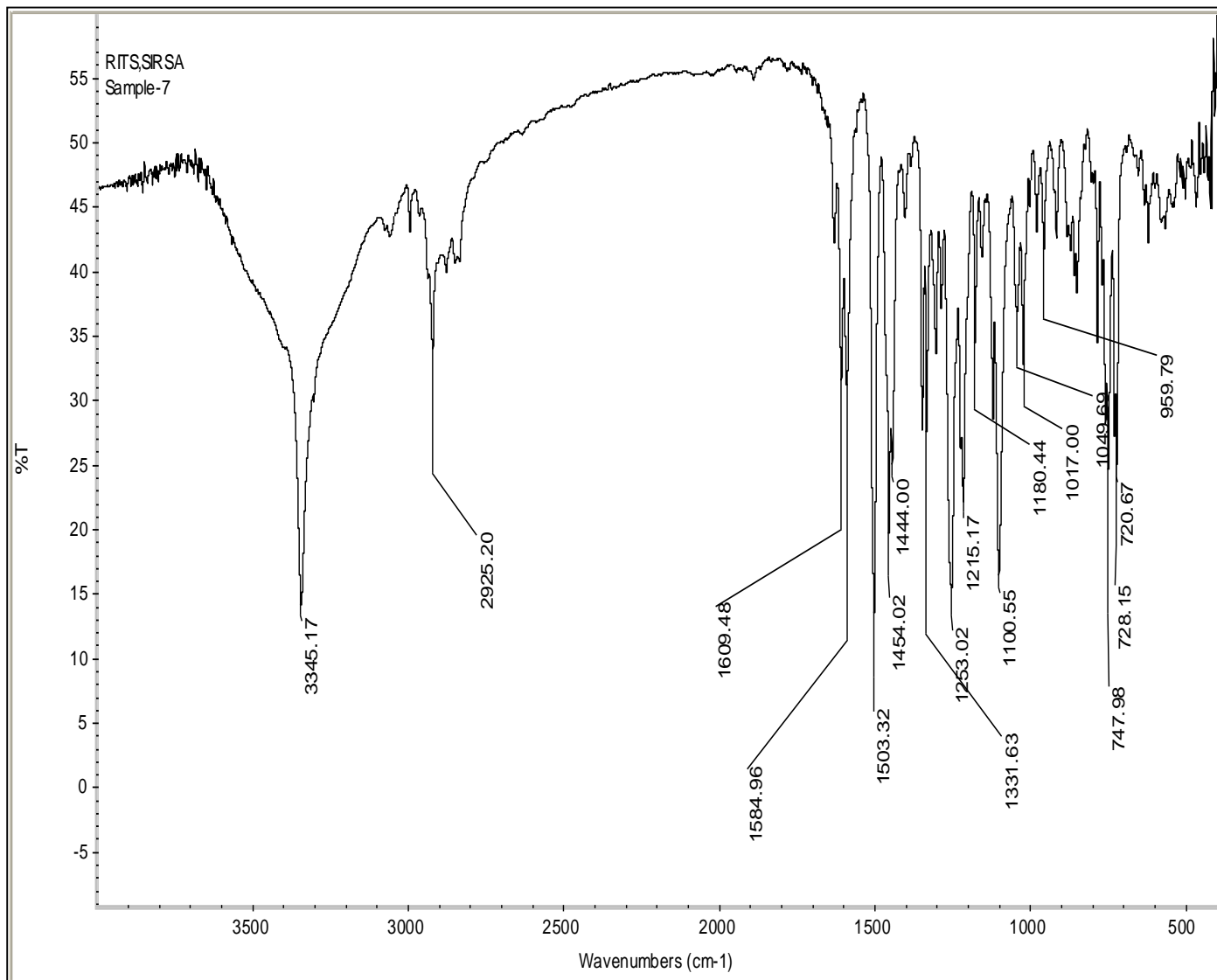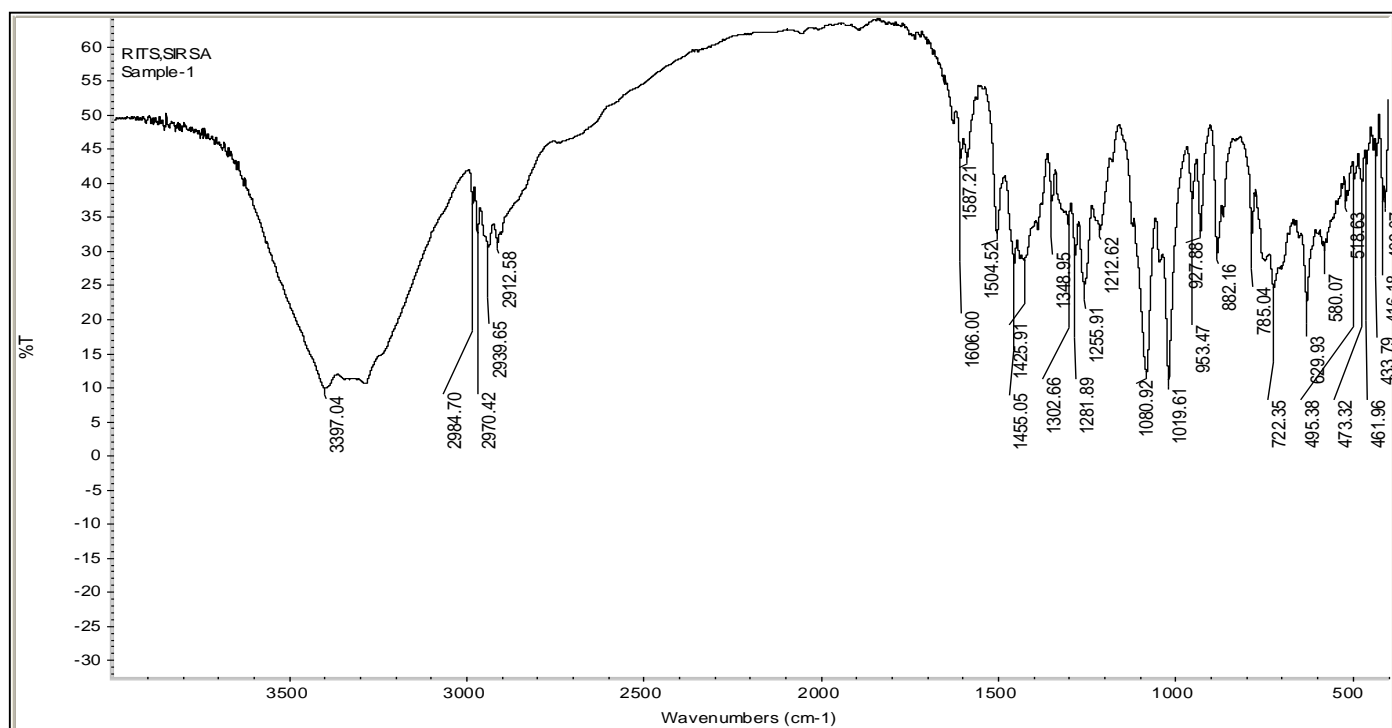
Fig 11: F.T.I.R. Spectra of Carvedilol

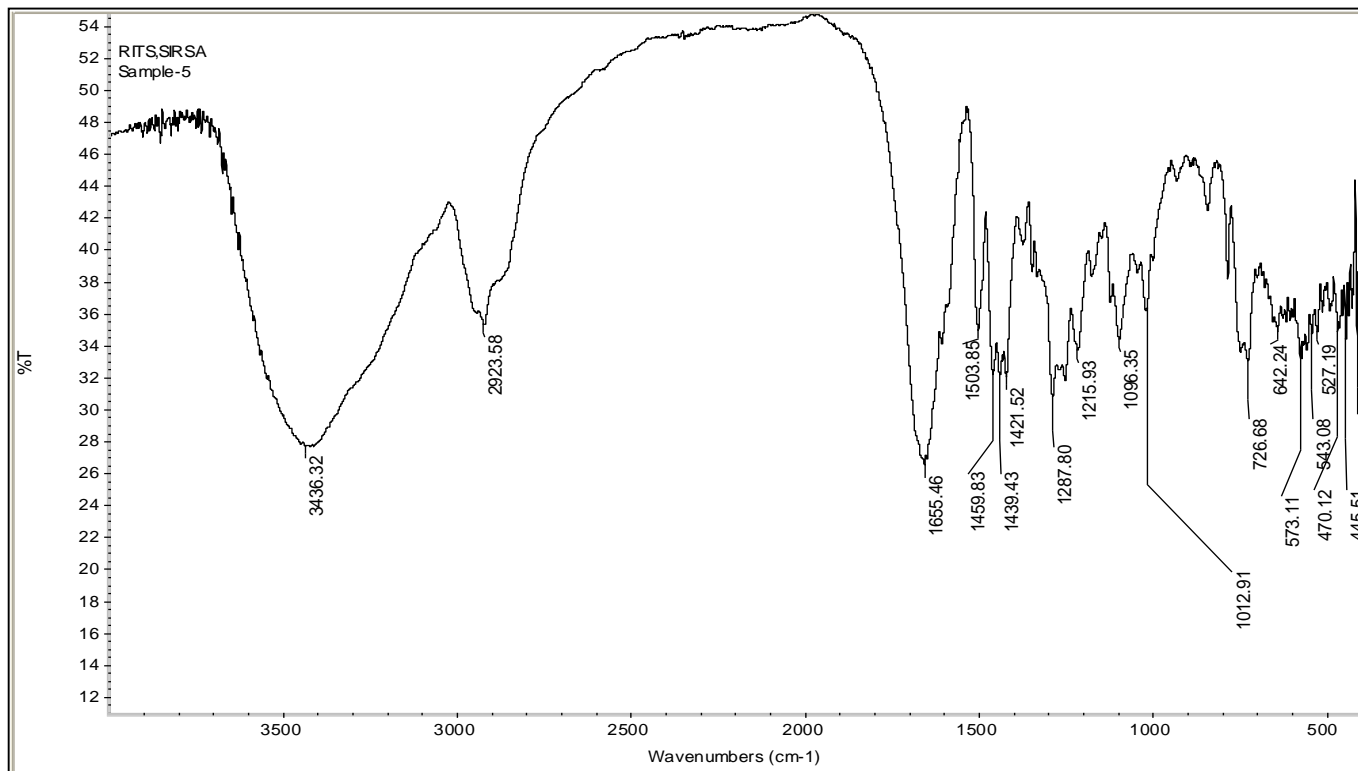**Fig 12:** F.T I.R. Spectra of Solid Dispersion with Mannitol

Fig 13: F.TI.R. Spectra of Solid Dispersion of Carvedilol with PVP K-30

Scanning Electron Microscopy (SEM)

SEM photomicrograph of pure carvedilol is shown in fig. given below. Analysis of SEM of carvedilol reveals that the drug exists in the crystalline from. From the photomicrographs of selected solid dispersions of carvedilol with mannitol or PVP K-30(fig. 38-39), illustrates through amorphous dispersion of drug in the matrix of mannitol and PVP K-30. Further it also limpid that the drug crystallinity is very significantly diminished, as is apparent from the deformation in the erstwhile crystalline lattices,

characteristics of the individual ingredients *viz.* carvedilol, mannitol and PVP K-30. This reduction in crystallinity has also been corroborated earlier using x-ray diffraction spectra (section 4.7.1.2) finally, it can be connoted that the solid dispersion of mannitol and PVP K-30 leads to distinct improvement in the dissolution profile of the drug. Ostensibly, this can be attributed to decreased crystallinity of the drug, as is vouched from characterization using XRD, DSC and SEM.
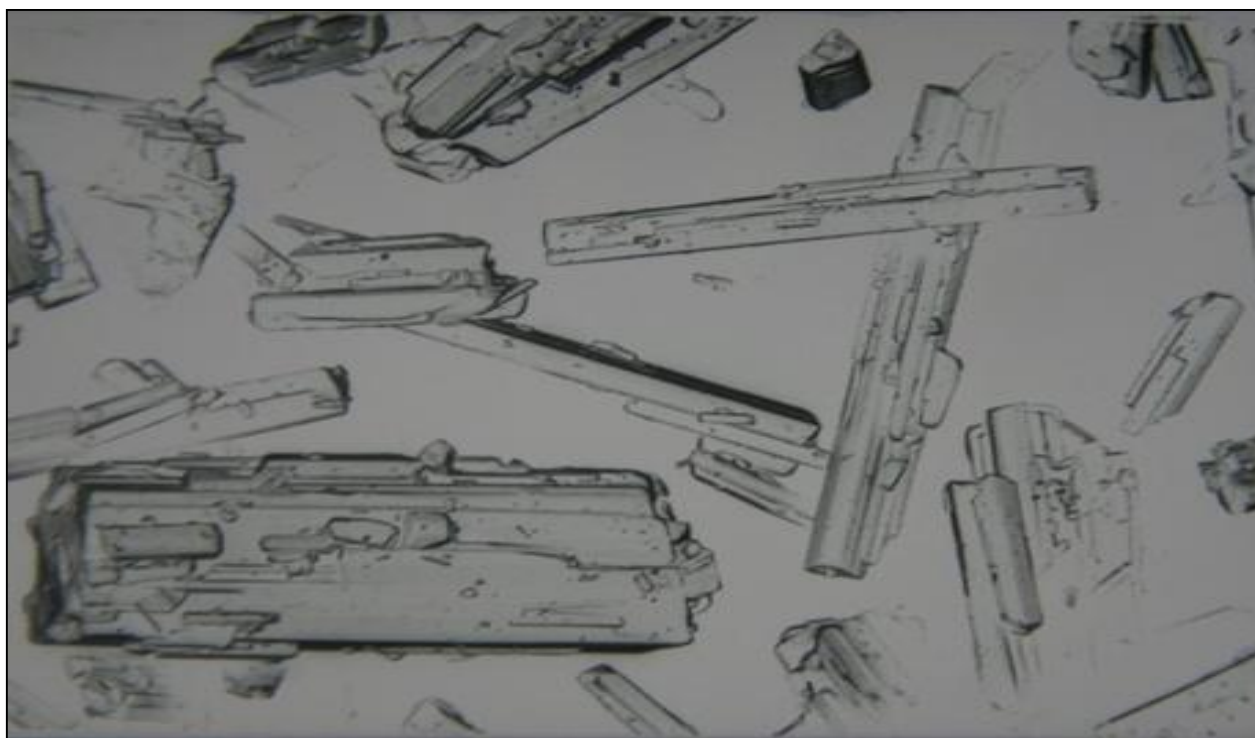

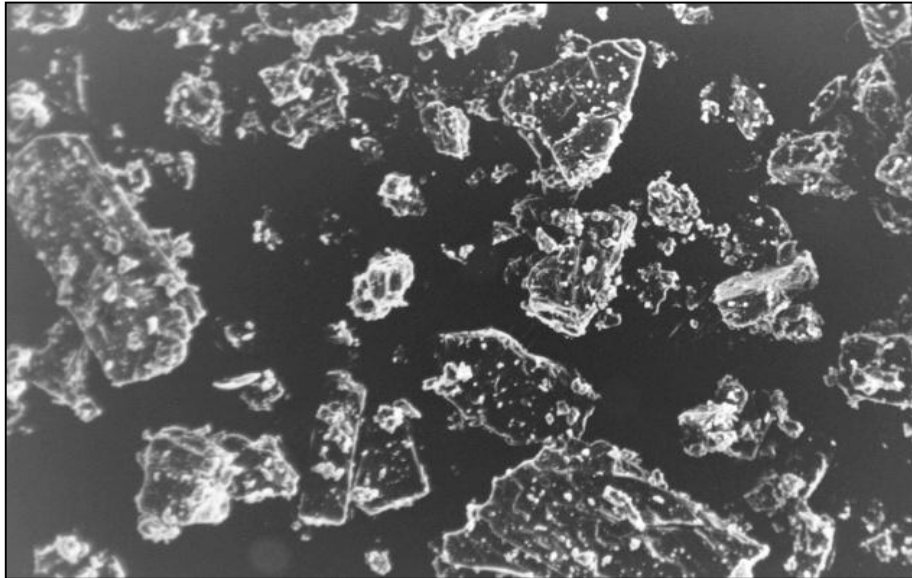**Fig 14:** Scanning Electron Microphotograph of Carvedilol

Fig 15: Scanning Electron Microphotograph of Solid Dispersion of Carvedilol with Mannitol
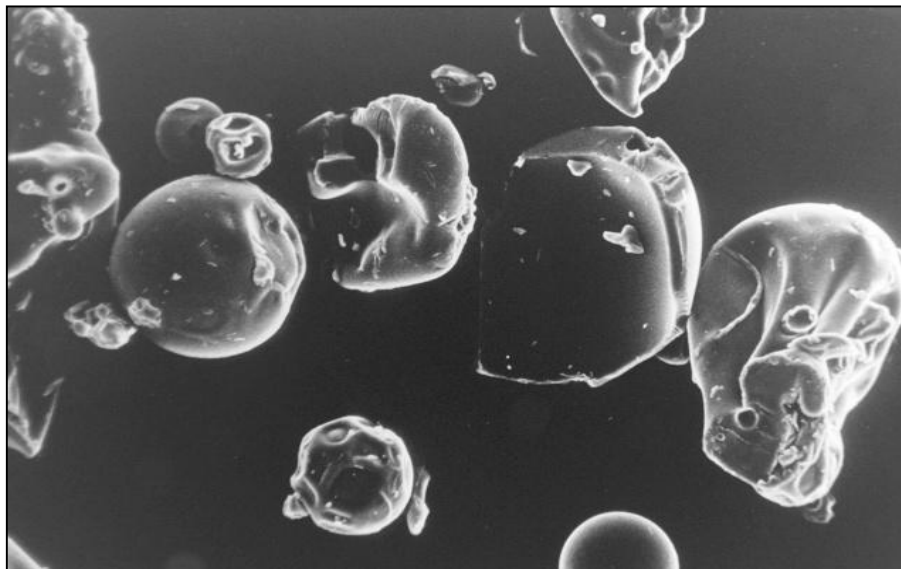

Fig 16: Scanning Electron Microphotograph of Solid Dispersion of Carvedilol with PVP K-30

Conclusion
Carvedilol is an important antihypertensive drug. The drug belongs to BCS class-II and hence its bioavailability often limited by its dissolution rate. Carvedilol-mannitol and carvedilol- PVP K-30 solid dispersions as well as physical mixtures in various ratios were formulated and studied for their *in-vitro* release performance. Solid dispersion of mannitol and PVP K-30 as effective and cost effective carriers, with carvedilol showed distinct superiority in a dissolution profiles vis-a-vis their corresponding physical mixture and that of pure drug. Best results have been obtained using carvedilol: Mannitol in ratio1:5 using solid dispersion technique. The significant improvement in the rate of release of carvedilol using carvedilol-mannitol solid dispersions formulation can help in appreciable reduction in the lag time of the drug absorption, characterized by high tmax values (120 minutes), thereby can improve the rate of bioavailability and onset of its therapeutic effects.

Conflict of Interest
The authors confirm that this article content has no conflict of interest

Acknowledgement

References
1. Amidon GL, Lennernäs H, Shah VP, Crison JR. A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. Pharmaceutical research. 1995; 12(3):413-20.
2. Ankunuru J. Oral drug delivery technology. Published by Pharma book Syndicate, Hyderabad, 2007, 116-117.
3. Arca HÇ, Mosquera-Giraldo LI, Pereira JM, Sriranganathan N, Taylor LS, Edgar KJ. Rifampin Stability and Solution Concentration Enhancement through Amorphous Solid Dispersion in Cellulose ω-Carboxyalkanoate Matrices. Journal of pharmaceutical sciences. 2018; 107(1):127-38.
4. Arias MJ, Gines JM, Moyano JR, Perez-Martinez JI, Rabasco AM. Influence of the preparation method of

solid dispersions on their dissolution rate: study of triamterene-D-mannitol system. International journal of pharmaceutics. 1995; 123(1):25-31.

5. Baghel S, Cathcart H, O'Reilly NJ. Understanding the generation and maintenance of supersaturation during the dissolution of amorphous solid dispersions using modulated DSC and 1 H NMR. International journal of pharmaceutics.. 2018; 536(1):414-25.

6. Beckett AH, Stenlake JB. Analysis of drugs in solid state in practical pharmaceutical chemistry. 1970; 3:64-66.

7. Bloch DW, Speiser PP. Solid dispersions- fundamentals and examples. Pharm. Acta. Helv. 1987; 62:23-27.

8. Brahmankar DM, Jaiswal SB. Biopharmaceutics and pharmacokinetics. A treatise. 2000; 1:5-75.

9. Breitenbach J. Melt extrusion: from process to drug delivery technology. European Journal of Pharmaceutics and Biopharmaceutics. 2002; 54(2):107-17.

10. Chaitanya P, Penta J, Devadasu VR, Venisetty RK, Vemula SK. Ezetimibe solid dispersions: formulation, development and in vitro evaluation. Open Journal of Advanced Drug Delivery. 2014; 2(1):90-103.

11. Chiou WL, Riegelman S. Pharmaceutical application of solid dispersion. J Pharm. Sci. 1971; 60:1281-1302.

12. Dua K, Ramana MV, Sara UV, Himaja M, Garg V, Agrawal A *et al*. Dissolution enhancement of aceclofenac through solid dispersions. The Indian Pharmacist. 2006; 5(48):70-2.

13. Gorajana A, Ying CC, Shuang Y, Fong P, Tan Z, Gupta J, Talekar M *et al*. Development of solid dispersion systems of dapivirine to enhance its solubility. Current drug delivery. 2013; 10(3):309-16.

14. Haser A, Cao T, Lubach JW, Zhang F. In Situ Salt Formation during Melt Extrusion for Improved Chemical Stability and Dissolution Performance of a Meloxicam–Copovidone Amorphous Solid Dispersion. Molecular pharmaceutics. 2018; 15(3):1226-37.

15. Kakran M, Sahoo NG, Li L. Dissolution enhancement of quercetin through nanofabrication, complexation, and solid dispersion. Colloids and Surfaces B: Biointerfaces. 2011; 88(1):121-30.

16. Leuner C, Dressman J. Improving drug solubility for oral delivery using solid dispersions. European journal of Pharmaceutics and Biopharmaceutics. 2000; 50(1):47-60.

17. Lindenberg M, Kopp S, Dressman JB. Classification of orally administered drugs on the World Health Organization Model list of Essential Medicines according to the biopharmaceutics classification system. European Journal of Pharmaceutics and Biopharmaceutics. 2004; 58(2):265-78.

18. Mamdouh MA, Badawi AA, Sakaran WS, Elshafeey AH, Elnahas OS. Different Solid Dispersion Techniques for Dissolution Enhancement Using Paracetamol as a Model Drug. International Journal of Pharmaceutical and Phytopharmacological Research. 2017; 4(4):231-7.

19. Maulvi FA, Dalwadi SJ, Thakkar VT, Soni TG, Gohel MC, Gandhi TR. Improvement of dissolution rate of aceclofenac by solid dispersion technique. Powder technology. 2011; 207(1-3):47-54.

20. Nagy ZK, Balogh A, Démuth B, Pataki H, Vigh T, Szabó B *et al*. High speed electrospinning for scaled-up production of amorphous solid dispersion of itraconazole. International journal of pharmaceutics. 2015; 480(1-2):137-42.

21. Park C, Meghani NM, Amin HH, Nguyen VH, Lee BJ. Patient-centered drug delivery and its potential applications for unmet medical needs. Therapeutic delivery, 2017; 8(9):775-90.

22. Sareen S, Mathew G, Joseph L. Improvement in solubility of poor water-soluble drugs by solid dispersion. International journal of pharmaceutical investigation. 2012; 2(1):12.

23. Serajuddin A, Sheen PC, Augustine MA. Improved dissolution of a poorly water-soluble drug from solid dispersions in polyethylene glycol: polysorbate 80 mixtures. Journal of pharmaceutical sciences. 1990; 79(5):463-4.

24. Serajuddin A. Solid dispersion of poorly water-soluble drugs: Early promises, subsequent problems, and recent breakthroughs. Journal of pharmaceutical sciences. 1999; 88(10):1058-66.

25. Shamsuddin MF, Ansari SH, Ali J. Development and evaluation of solid dispersion of spironolactone using fusion method. International journal of pharmaceutical investigation. 2016; 6(1):63.

26. Shargel L, Yu AB. Applied Biopharmaceutics and pharmacokinetics (5th Ed.). New Yark: McGraw-Hill, 2005, 453-498.

27. Sharma D, Soni M, Kumar S, Gupta GD. Solubility enhancement–eminent role in poorly soluble drugs. Research Journal of Pharmacy and Technology. 2009; 2(2):220-4.

28. Sharma DK. Solubility enhancement strategies for poorly water-soluble drugs in solid dispersions: A review. Asian Journal of Pharmaceutics (AJP): Free full text articles from Asian J Pharm. 2016, 1(1).

29. Vasconcelos T, Sarmento B, Costa P. Solid dispersions as strategy to improve oral bioavailability of poor water soluble drugs. Drug discovery today. 2007; 12(23-24):1068-75.

30. Verma S, Rudraraju VS. Disintegration mediated controlled release supersaturating solid dispersion formulation of an insoluble drug: design, development, optimization, and in vitro evaluation. AAPS Pharm SciTech. 2015; 16(1):85-97.

31. Vidyadhara S, Srinivasa Babu P, Swapna Sundari P, Tusha Rani M. Solid dispersion: An approach to improve solid formulation development. Pharma Bio world. 2004, 70-6.

32. Vo CL, Park C, Lee BJ. Current trends and future perspectives of solid dispersions containing poorly water-soluble drugs. European Journal of Pharmaceutics and Biopharmaceutics. 2013; 85(3):799-813.

33. Wang W, Kang Q, Liu N, Zhang Q, Zhang Y, Li H *et al*. Enhanced dissolution rate and oral bioavailability of Ginkgo Biloba extract by preparing solid dispersion via hot-melt extrusion. Fitoterapia. 2015; 102:189-97.

34. Wyatt DA. Taking poorly water soluble compounds through discovery. Bulletin technique-Gattefossé report. 1999; 92:31-9.

35. Paaver U. New perspectives for the amorphization and physical stabilization of poorly water-soluble drugs and understanding their dissolution behavior (Doctoral dissertation).