International Journal of ChemTech Research
CODEN (USA): IJCRGG, ISSN: 0974-4290, ISSN(Online):2455-9555
Vol.10 No.4, pp 160-171, 2017

Formulation and Evaluation of Solid Dispersion of Furosemide in Poly vinyl Pyrollidone K 30

Meenakshi[1], Azhar Danish Khan[2]*

[1]Department of Pharmaceutics, College of Pharmaceutical Sciences, R.K.G.I.T Ghaziabad .(U.P), India
[2]Dept of Pharmaceutics RamEesh Institute of Vocational and Technical Education , Greater Noida (U.P), India

Abstract : This investigation was carried out to determine if a solid dispersion of Furosemide in Poly vinyl pyrollidone (PVP K-30) will enhance the dissolution and permeation properties of the drug.Solid dispersion of Furosemide in PVP K 30 was prepared in ratios by Solvent Evaporation Method amongst which 1:4 was the optimized batch. Permeation study was also performed. In this case, the solid dispersion was characterized by Fourier transform Infrared spectroscopy, differential scanning calorimetry (DSC) to ascertain if there were any physicochemical interactions between drug and carrier that would effect dissolution. Mouth dissolving tablets containing solid dispersion were formulated. The dissolution studies were performed at 37$\pm$ 0.5^0 C and 50 rpm in simulated gastric fluid (pH 6.8).
FTIR spectroscopy and DSC showed a change in crystal structure toward an amorphous form of Furosemide. Dissolution data indicated that Furosemide dissolution was enhanced. FTIR,DSC spectroscopy and dissolution studies indicated that solid dispersion formulated in 1:4 ratio showed an increase in dissolution .Solid Dispersion technique can be used to improve the dissolution of Furosemide along with its permeation.
Keywords : Solid dispersion, Furosemide, Poly vinyl pyrollidone K-30, 0.1% Sodium lauryl sulphate, physicochemical characterization.

Introduction

Furosemide (FRMD) is 5-(aminosulphonyl)-4-chloro-2-[(2-funayl-methyl) amino] benzoic acid, and it is a potent high ceiling (loop) diuretic mainly used in treatment of hypertension. The drug has been classified as a class IV drug as per the biopharmaceutical classification system (BCS) as a result of its low solubility and oral bioavailability is its solubility[1, 2,3].The present work aims to evaluate the potentials of the solid dispersion technique for the development of mouth dissolving tablets of FRMD using Poly vinyl pyrollidone K 30, as a hydrophilic carrier[4, 5].

Oral bioavailability of a drug depends on its solubility and/or dissolution rate, and dissolution may be the rate determining step for the onset of therapeutic activity. Therefore efforts to increase drug dissolution of drug are often needed. Salt formation, micronization and addition of solvent or surface active agents are the methods to improve dissolution. Solid dispersion is one the such methods and it involves a dispersion of one of one or more active ingredients in an inner carrier or matrix in solid state prepared by solvent evaporation method[6, 7]. This technique has been used for a wide variety of poorly soluble drugs such as carbamazepine, celecoxib , Ibuprofen, Meloxicam, Nevirapine, Terbinafine, Rofecoxib, Valdecoxib.

The present work aims to evaluate the potential of solid dispersion technique for development of mouth dissolving tablets of FRMD using PVP K 30 as the hydrophilic carrier[5, 6]. The method used is Solvent evaporation method in which both the drug and the Hydrophilic polymer are dissolved in a common solvent later allowed for the evaporation of the solvent so the residue left over is the solid dispersion. Later these are analzed through the analytical tools such as Fourier Transform infrared (FTIR), Differential scanning calorimetry. Furthermore the dissolution was investigated.

Experimental

Materials and Method

Materials

Furosemide was gift sample from Hem Deep Organics Pvt. Ltd mfg of Bulk drugs and intermediates, Plot No.3801/2, G.I.D.C., Ankleshwar. Dist. Bharuch , Gujarat , India. Polyvinyl pyrollidone K 30 and Ethanol was used.

Preparation of Furosemide-PVP K 30 solid dispersion

A mixture (20mg) of Furosemide and PVP K 30 (1:4) by weight, respectively. The polymer was first dissolved in ethanol, to get a clear solution later the drug was dissolved in the polymer solution. The resultant mixture was than stirred to evaporate the volatile substance. Than the material was passed through sieve no 60. Than the formed material was stored in the desiccator till the further use. Therefore the solid dispersion was used to prepare the mouth dissolving tablets[5, 11].

Evaluation

Content uniformity study:

The solid dispersions containing an equivalent amount of 10 mg of Furosemide was added to a volumetric flask (25 ml) containing phosphate buffer (pH 6.8), the flask was shaken for 15 min and final volume was made with phosphate buffer (pH 6.8). The sample was filtered and assayed for Furosemide spectrophotometrically (Shimadzu 1700 at 227.4 nm) [15].

Solubility studies:

Solubility measurement were performed according to Higuchi and corners method (Higuchi and corners.1965): The solubility of solid dispersions is usually determined by the equilibrium solubility method, which employs a saturated solution of the material, obtained by stirring an excess of material in the solvent for a prolonged period (24 hr) until equilibrium is achieved. The solutions were filtered and absorbance was checked at 227.4 nm using spectrophotometer.

Fourier transform infrared (FTIR) spectroscopy

FTIR spectra were recorded on samples prepared in potassium bromide (KBr) disksusing a Shimadzu Corporation facility (model - 8400S) from Punjab. Samples were prepared in KBr disks in a hydrostatic press at6-8 tons pressure. The scanning range was500 to 4000 cm.

Differential scanning calorimetry (DSC)

The DSC analysis was performed with Universal V4.5A TA Instruments, from IIT Delhi. It was found that the melting point of the Drug-Polymer Complex was lower in comparison of the pure Drug. This shows Amorphization of the Drug in Solid Dispersion.

Dissolution rate studies

The dissolution was studied with accurately weighed amount of the formulations(containing approx. 20 mg of furosemide)using a USP apparatus II in 900 ml of simulated gastrointestinal fluid (SGF, pH 6.8)for one hour. The rotational speed of thepaddle was set at 50 rpm at 37 ± 0.5ºC.Aliquots (5ml each) were withdrawn at

predetermined time intervals for 1h; sink conditions were maintained. The samples were analyzed for drug content using a double beam UV spectrophotometer at 227.4 nm.

Tablet preparation and characterization

Tablets containing an equivalent of 110 mg of Furosemide (SD2) were compressed on a 16-station single rotary tabletting press (Type –CMD3 – 16, using an 8-mm standard flatpunch by direct compression technique, at a compression pressure of 6 tons. The tablet formulation were code as S1, S2, S3, S4, S5, S6, S7 which were at different ratios of super disintegrant of 7, 8, 9, 10, 11 12, 13 respectively. Amongst all S6 is the best batch. It contains 110 mg of Furosemide, 24 mg of Sodium Starch Glycolate, 25 mg of Mannitol, 10 mg of starch, 25 mg of Microcrystalline cellulose, 2 mg of Magnesium Sterate, 2 mg of Talc, and 2mg of sodium lauryl sulphate and was punched of 200 mg tablet. Tablet was evaluated for hardness (Pfizer/Monsanto Hardness tester), Friability(Roche friabilator), weight variation, and drug content. In vitro dissolution studies were performed among different batches and a comparative study was performed as in fig.3.

Table 3. Comparative study of Mouth dissolving tablet dissolution

Time(min)	% drug release of S1	% drug release of S2	% drug release of S3	% drug release of S4	% drug release of S5	% drug release of S6	% drug release of S7
0	0	0	0	0	0	0	0
2	40.099	25.99	25.248	28.218	39.356	34.901	45.297
4	56.658	50.639	60.289	58.078	54.427	68.511	58.915
6	62.17	61.316	65.821	61.37	61.411	88.197	68.152
8	69.196	69.823	69.897	87.698	68.432	98.337	86.349
10	68.833	76.147	79.934	88.923	91.085	100.363	91.279
15	65.495	78.791	81.114	90.153	95.297	99.427	99.204

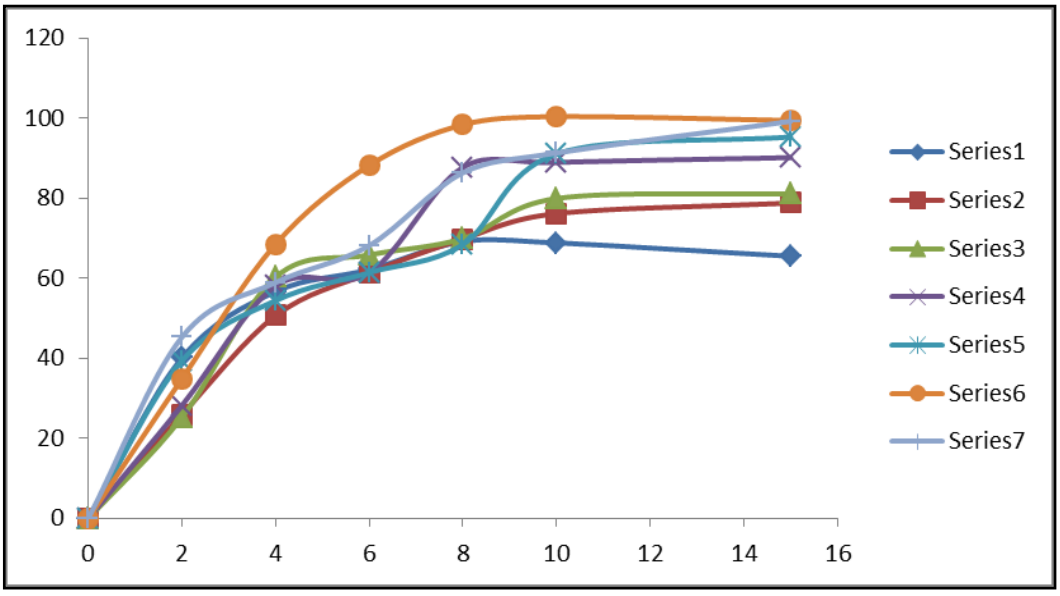

Figure 3 : In-vitro dissolution S1 (♦), S2 (■), S3 (▲), S4 (×), S5 (X), S6 (●), S7 (+)

Permeation studies:

Permeation studies were performed using using 0.1%, 0.5%, 1%.Sodium lauryl sulphate as the permeation enhancer. Amongst which 1% showed the best result. The assembly was set using Franz diffusion cell. In which the donor was filled with 15 ml drug isotonic solution in pH 6.8. And the recipient was filled with the same isotonic solution of pH6.8. The git membrane of rat was used for the permeation study under the **College registration code-992/a/06/CPCSEA**. The sample was withdrawn at regular intervals and sink

condition was maintained. The samples were analyzed for drug content using a double beam UV spectrophotometer at 227.4 nm. As in Tab 2 and Fig 2.

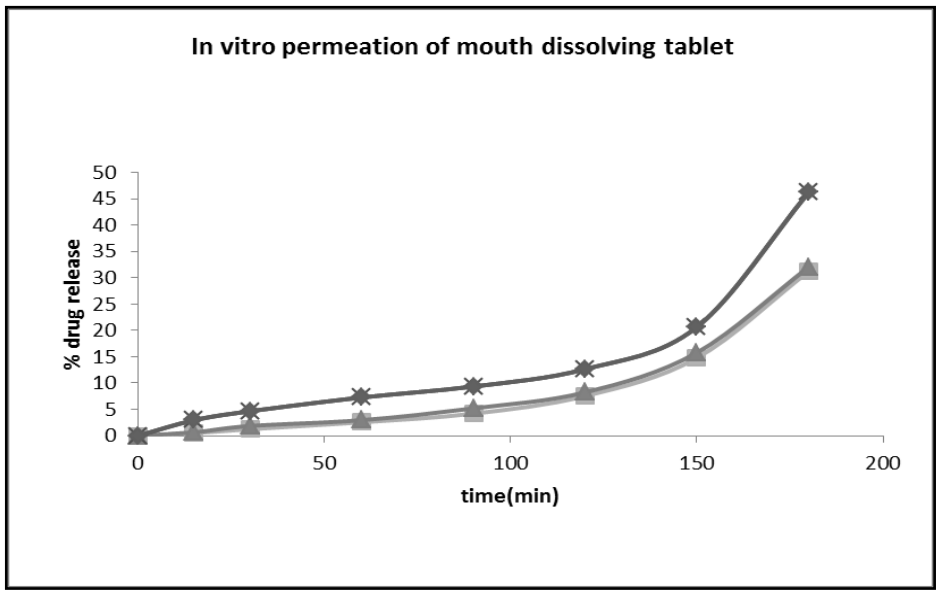

Figure 2 : In-vitro permeation Furosemide(▲), Solid dispersion(■), mouth dissolving tablet(♦).

Table 2. Comparitive study of permeation-

Time(min)	% Cum release of Furosemide	% Cum release of solid dispersion	% Cumlative release of mouth dissolving tablet
0	0	0	0
15	0.5	0.65	2.95
30	1.24	1.85	4.65
60	2.56	2.96	7.27
90	4.2	5.2	9.35
120	7.54	8.24	12.65
150	14.78	15.78	20.64
180	31.25	32.05	46.25

Results

FTIR spectroscopy

IR spectra of Furosemide and its binary systems with PVP K 30 are presented in Figure 1.Pure Furosemide spectra showed sharp characteristic peaks at 3398.34, 3122.54,1665, and 1560 cm–1. See Fig 4,5,6.The above characteristic peaks appear in the spectra of all binary systems at the same wave number indicating no interaction between the drug and the carrier (PVP K 30).

Table 4: Evaluation Properties of Mouth dissolving tablets.

Evaluation Parameter	S1	S2	S3	S4	S5	S6	S7
Weight variation	Within Limit	Within Limit	Within Limit	Within Limit	Within Limit	Within Limit	Within Limit
Hardness (kg/cm^2)	2.4	2.4	2.5	2.5	2.4	2.5	2.5
Friability (%)	0 .61	0.62	0.60	0.62	0.62	0.60	0 .61
Uniformity of Content (%)	98.32	98.30	98.61	98.92	98.61	98.92	98.30
Water absorption rate	70.6	74.0	74.5	76.6		74.0	74.5

					70.6		
Wetting time (sec)	24	25	23	22	25	23	22
Disintegration Time (sec) in vitro	24	23	24	24	23	22	25
In vitro drug release (%)	65.495	78.791	81.114	90.153	95.297	99.427	99.204

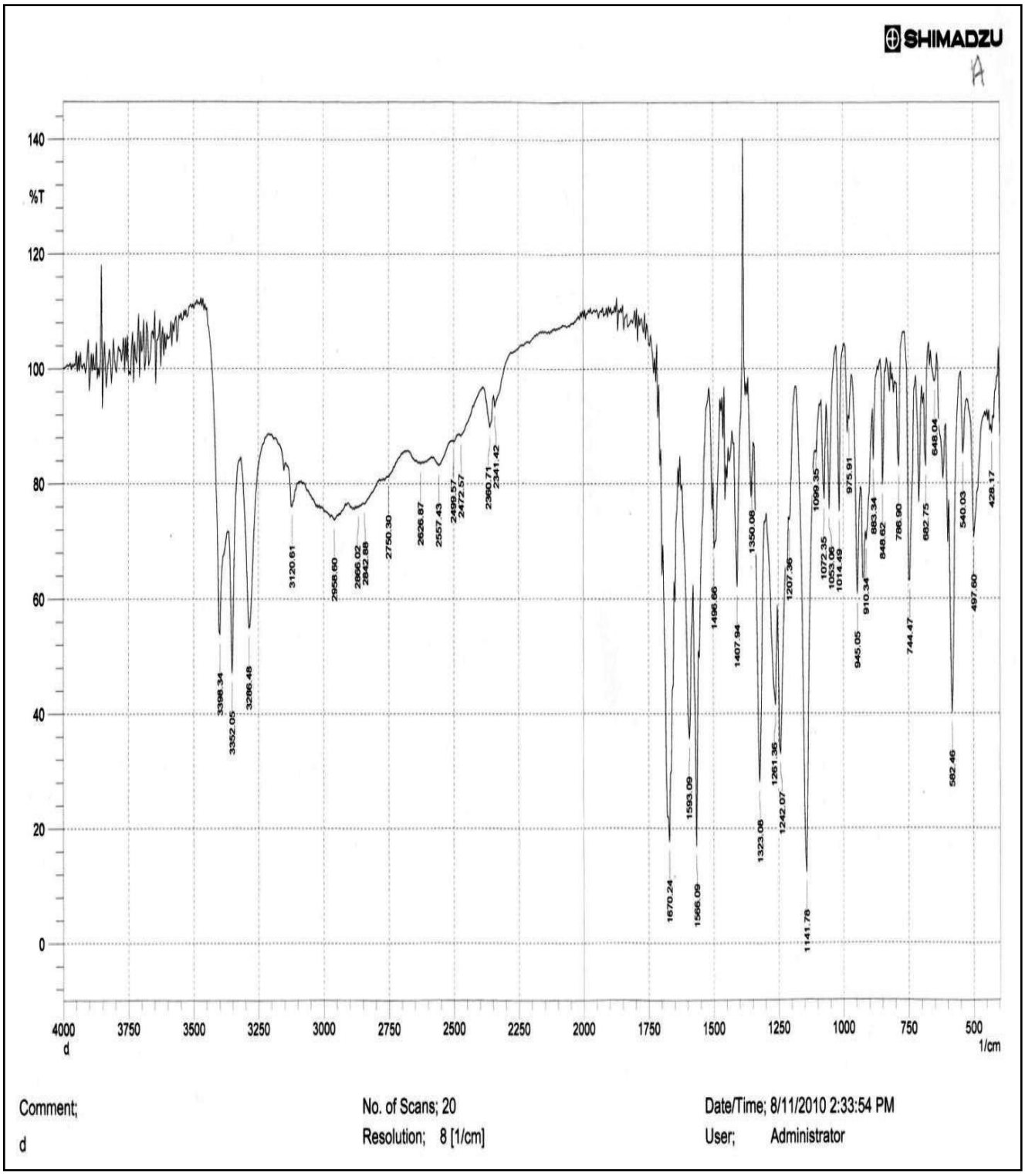

Figure 4. **Fourier transform infrared (FTIR) spectroscopy of Furosemide (F).**

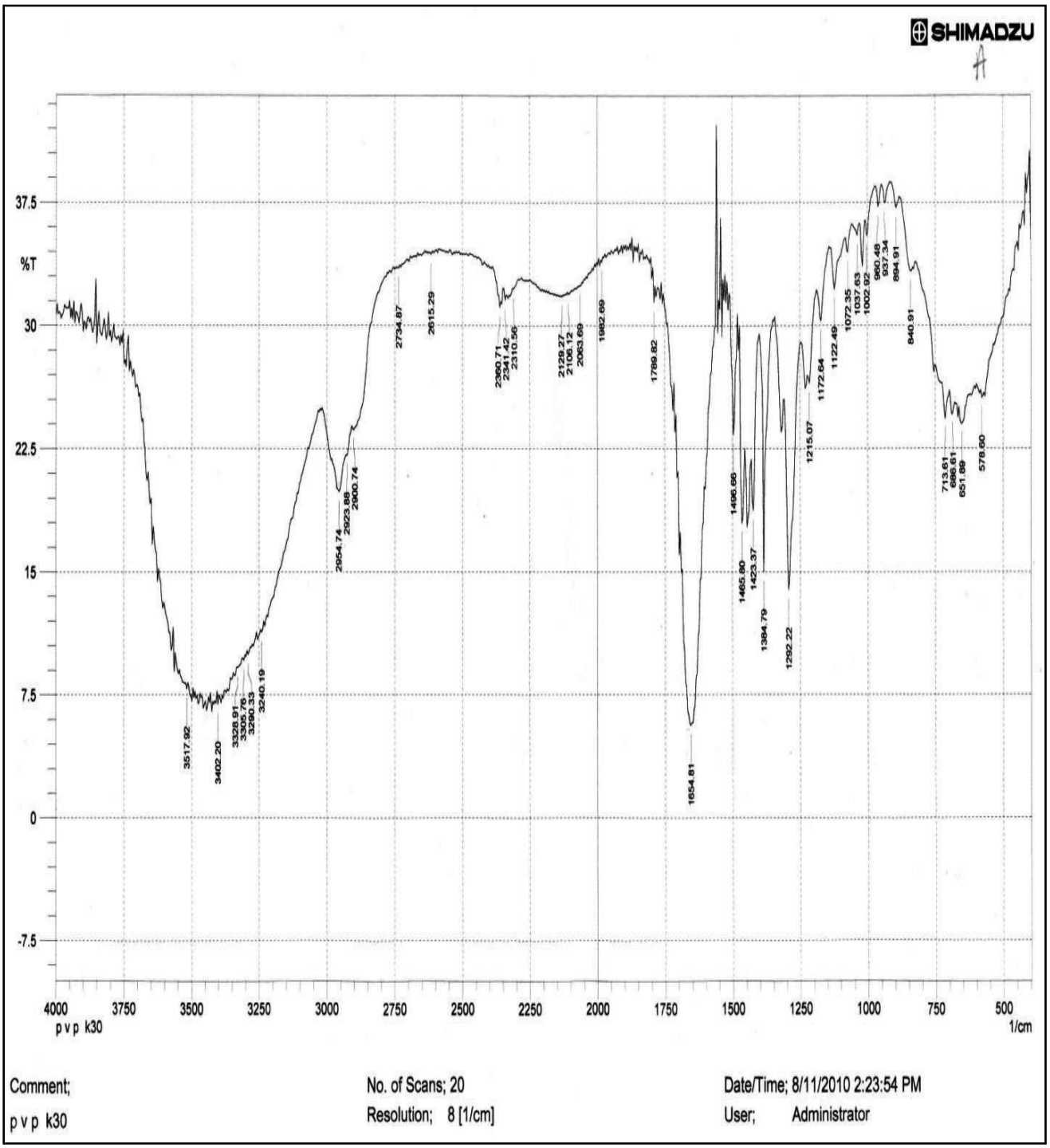

Figure 5. Fourier transform infrared (FTIR) spectroscopy of Polyvinyl pyrrolidone K30 (PVP K30).

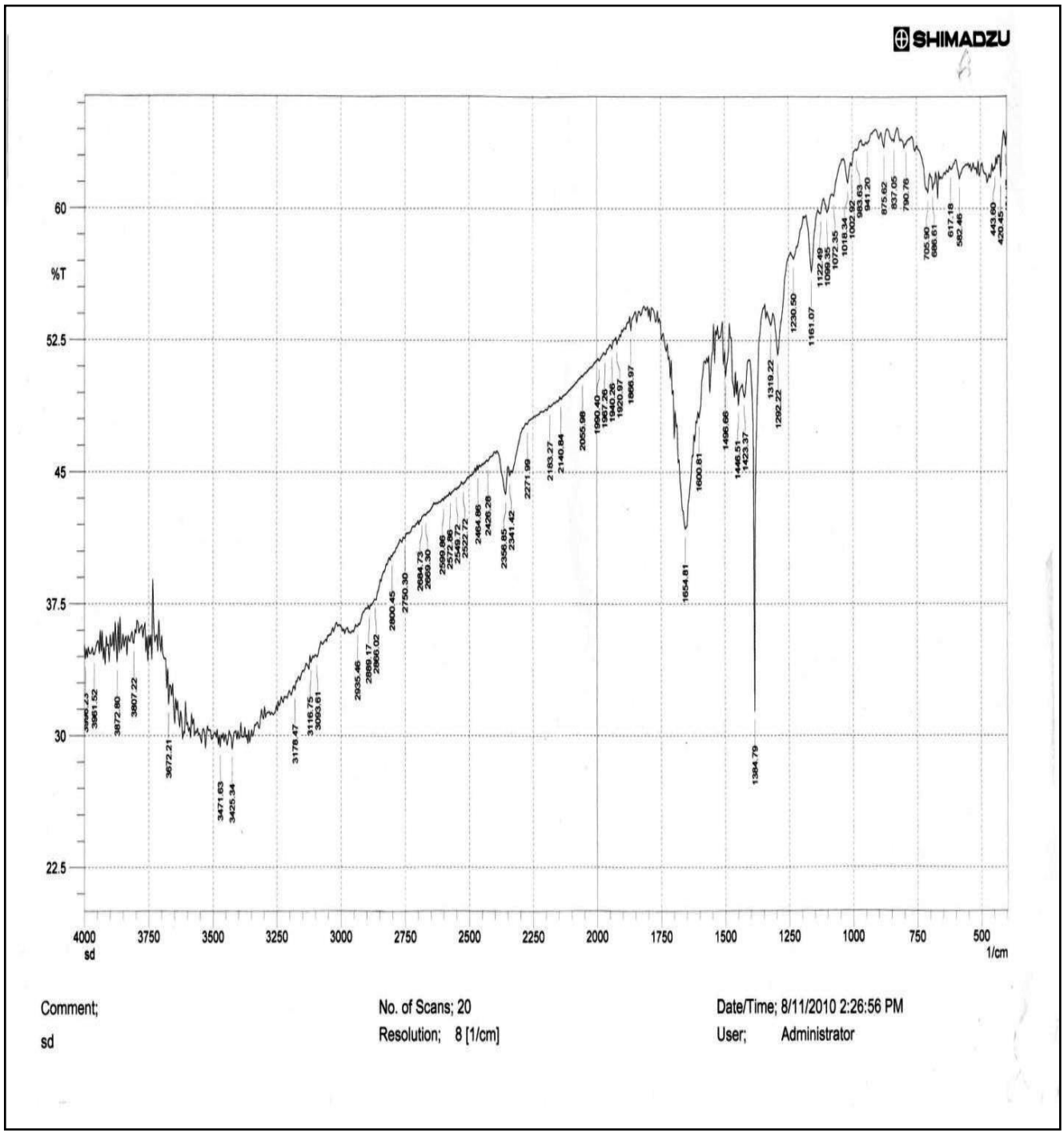

Figure 6. Fourier transform infrared (FTIR) spectroscopy of Solid dispersion (SD)

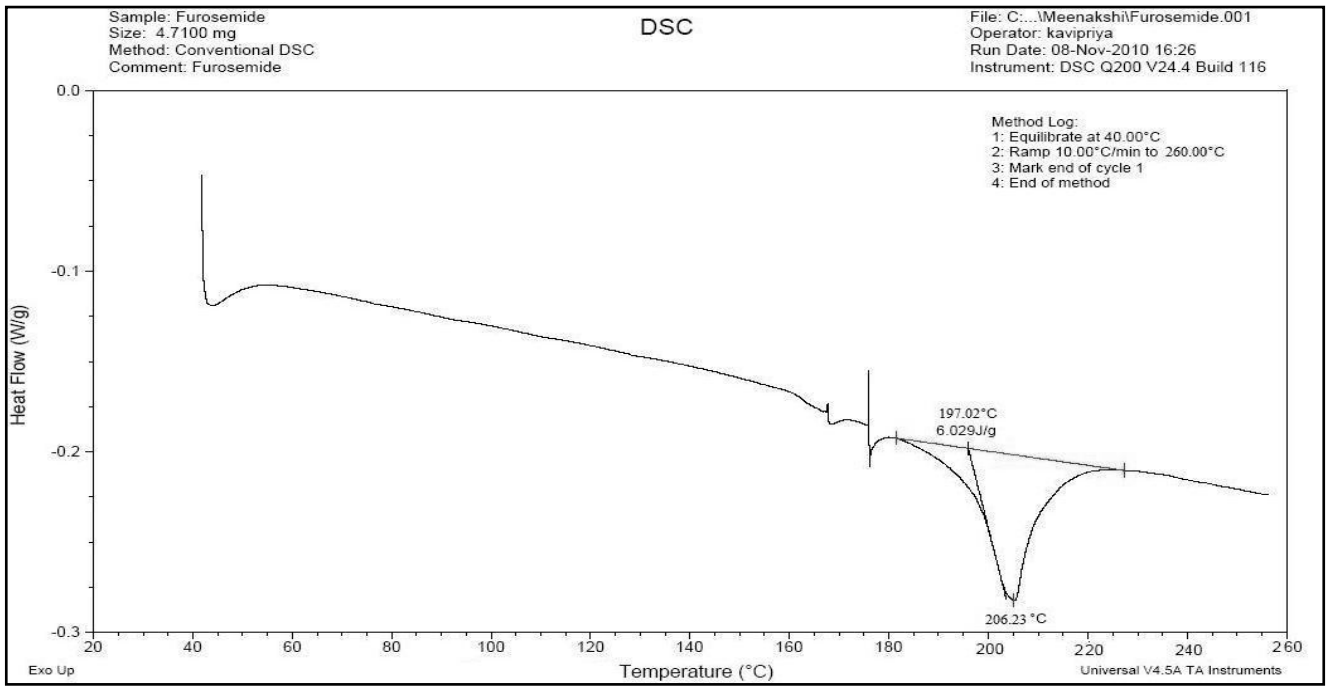

Figure 7: Differential Scanning Calorimetry of Bulk drug Furosemide (F)

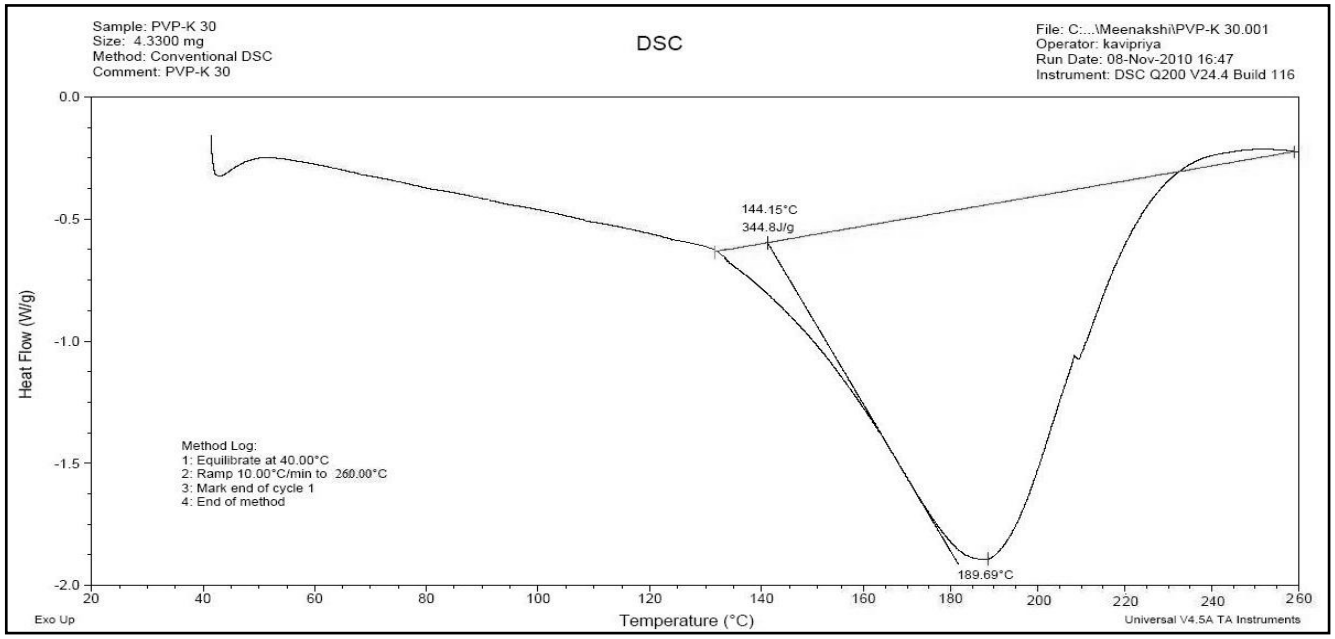

Figure 8: Differential Scanning Calorimetry of Polyvinyl pyrrolidone K30 (PVP K30)

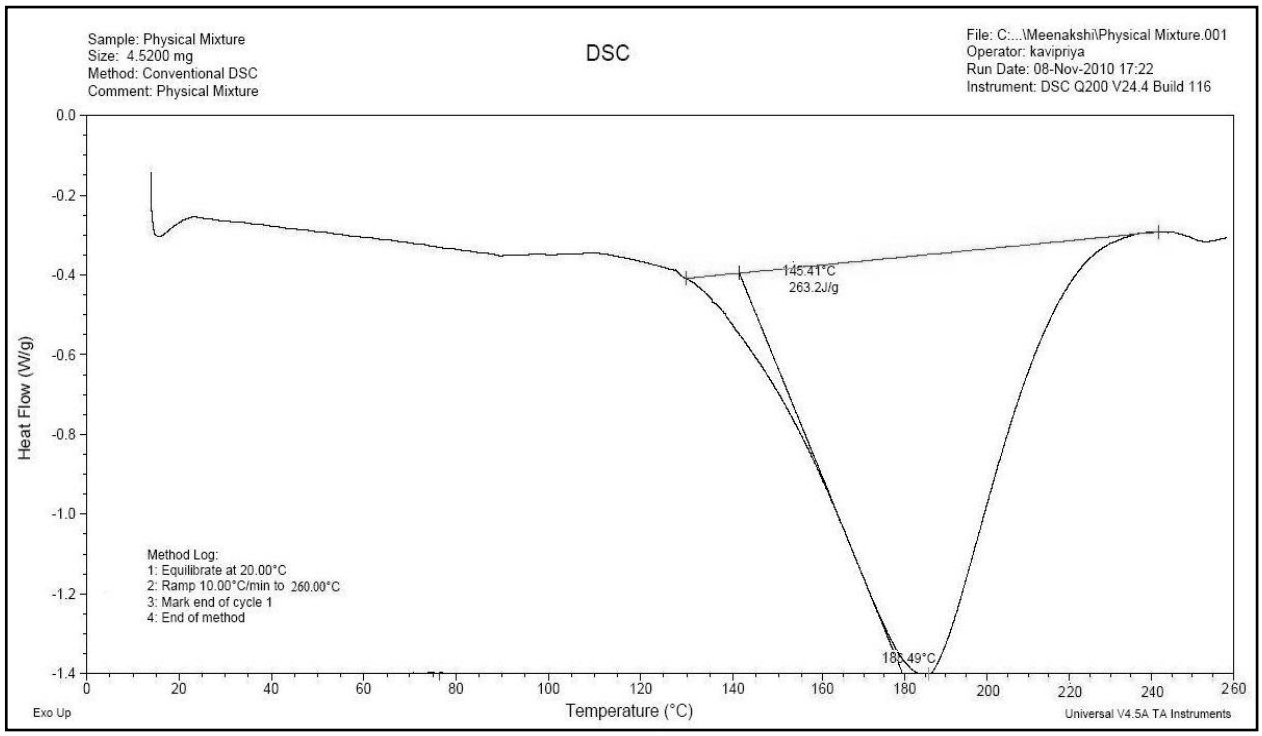

Figure 9: Differential Scanning Calorimetry of Poly vinyl pyrrolidone K30 (PVP K30)

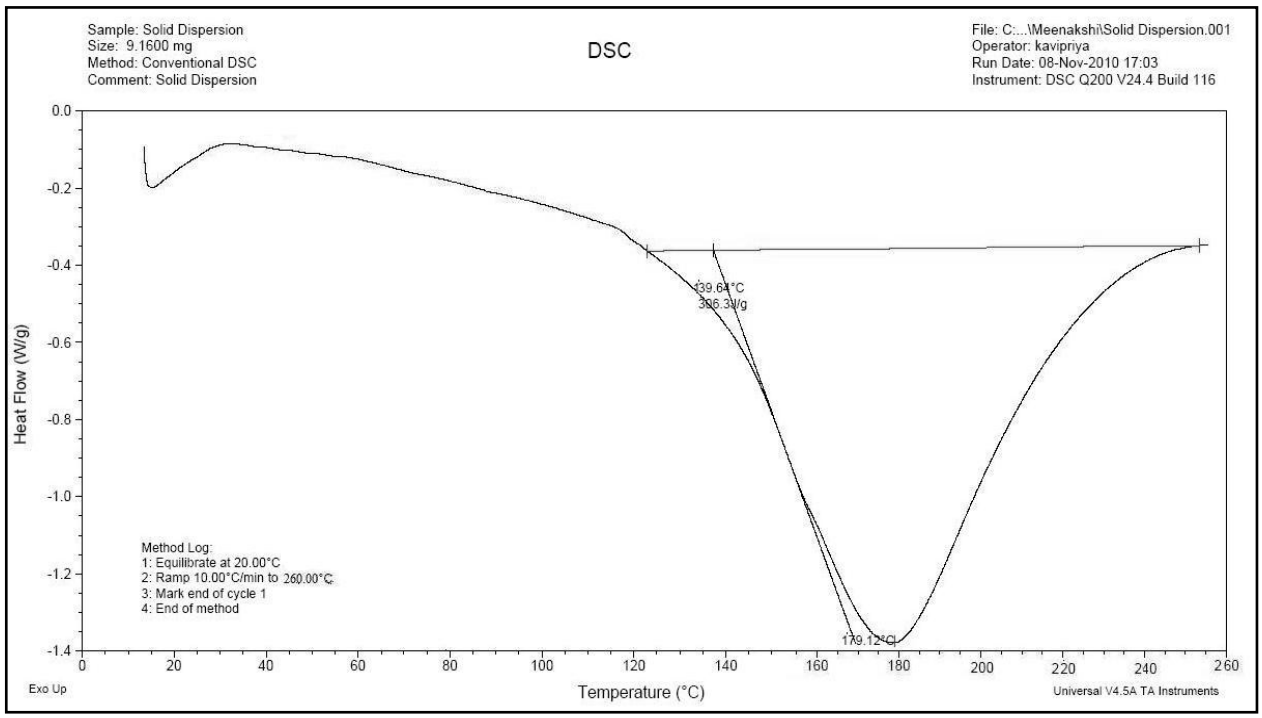

Figure 10: Differential Scanning Calorimetry of Solid dispersion (SD)

Differential scanning calorimetry (DSC)

DSC Thermograms of Furosemide, PVP K30, Physical mixture of both as well as their solid dispersions prepared by Solvent evaporation method are shown in Figure 7, 8,9,10. Furosemide exhibited a characteristic, sharp exothermic peak at 206.23^{o}C which is associated with the melting point of the drug and indicates the crystalline nature of the drug; degradation was indicated by anendothermic peak at 280.2 ^{o}C. However, the characteristic exothermic peak, corresponding to drug melting was broadened and shifted towards a lower temperature to 179.12^{0}C with reduced intensity in both physical mixtures and solid dispersions. DSC

studies also showed that there no interaction between drug and carrier at a molecular level in both the solid dispersions and physical mixtures.

Dissolution studies

The dissolution profiles of the pure drug, carrier (PVP K 30) and binary systems are presented in Figure 1 and Tab 1. It is evident that the solid dispersion (SD) technique improved the dissolution rate of the drug to a great extent .The results indicate that SD2 (101.73% of drug dissolved in 60 min) showed the highest dissolution rate, followed by SD1 with 85% of drug dissolved over the same period. Physical mixtures (PM) also improve dissolution rate significantly. The PM2 showed an increment of 80% and that PM1 increased by 53%. The order of dissolution rate is SD2 >SD1 > PM2 > PM1 > drug alone. To formulate a tablet of furosemide, the SD2binary mixture was selected based on its *invitro* dissolution performance. S6 tablets showed the fastest disintegration (24 seconds)and this is attributed to inclusion of the disintegrant, Sodium starch glycolate, in the formulation. *In vitro* dissolution studies for S6 confirmed the results obtained with solid binary mixtures.S6 tablets, like the corresponding binary mixture, showed good dissolution (100%) in 12 min. So this indicates.

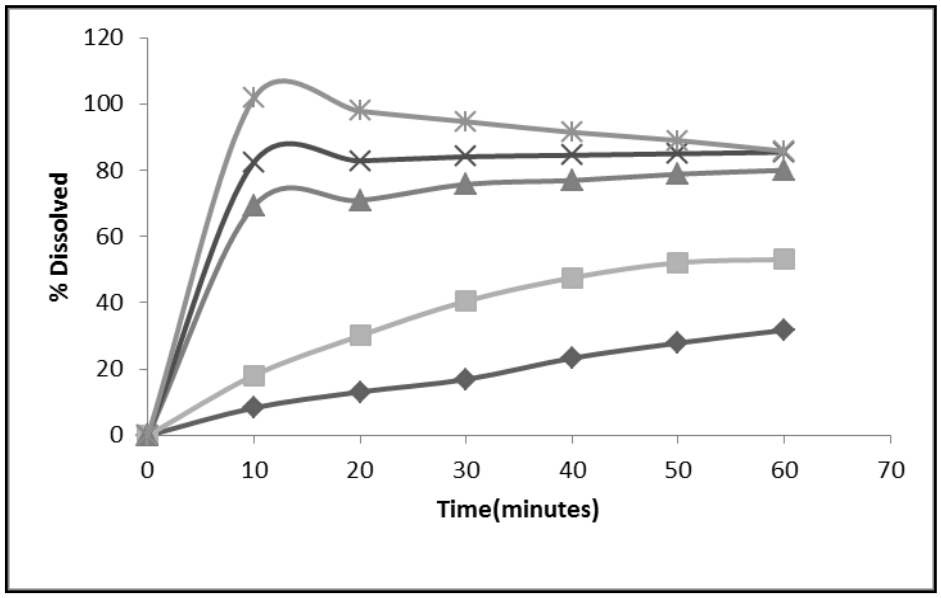

Figure 1: Dissolution profiles of Furosemide and its binary systems with PVP K 30. (♦)- Furosemide, (■) - PM 1, (▲) - PM 2, (×) - SD 1, (X)-SD 2

Table 1. Percent drug release of Bulk drug (F), Physical mixture (PM 1), Solid dispersion (SD1), (PM2), (SD2).

Time(min)	% Drug release of Furosemide	% Drug release of PM1	% Drug release of SD1	% Drug release of PM2	%Drug release of SD2
0	0	0	0	0.000	0.000
10	8.316	18.119	82.426	69.282	101.733
20	13.115	30.101	82.884	70.929	97.842
30	16.900	40.515	84.084	75.777	94.670
40	23.306	47.570	84.546	76.936	91.477
50	27.889	52.139	85.008	78.842	89.006
60	31.755	53.092	85.470	80.014	85.776

Discussion

The solid dispersion was prepared and characterized and the results showed that 1:4 solid dispersion (SD2) had a higher dissolution profile compared to other formulations. The order of dissolution rate is SD2 > SD1 > PM2> PM1 > FRMD.As shown in FTIR spectroscopic studies, the spectra of pure drug, Furosemide and solid dispersion were similar and the peak for pure Furosemide was also appeared in all the spectra of the binary mixtures. Thus, there was no interaction between the drug and the carrier (PVP K 30). DSC studies, on the basis of the melting peak of Furosemide (206.23^0C),also indicate that there was not interaction between the drug and carrier. However, the characteristic melting peak broadened and shifted toward a higher temperature with reduced intensity for both the physical mixtures as well as solid dispersions. This may be attributed to high polymer concentration and uniform distribution of the drug in the crust of the polymer, resulting incomplete miscibility of the molten drug in the polymer. Enhancement of the dissolution of Furosemide from the solid dispersions can be ascribed to several factors which affect the mechanism of dissolution rate improvement in solid dispersion. Lack of Crystallinity, i.e., Amorphization, increased Wettability and Dispersibility and particle size reduction are considered to be important factors for dissolution rate enhancement. As indicated by the dissolution data of the physical mixtures, improvement could be attributed to higher wettability and dispersibility. Dry mixing of drug with a hydrophilic carrier results in greater wetting and increases surface available for dissolution by reducing interfacial tension between hydrophobic drug and is solution media.

Conclusion

This study shows that the dissolution rate of Furosemide can be enhanced considerably by formulating in it as a solid dispersion in PVP K 30 using a solvent evaporation method. Incorporation of superdisintegrants in the solid dispersions played a critical role in dissolution enhancement. It may be feasible to prepare suitable formulations of Furosemide solid dispersions as mouth dissolving tablets.

Acknowledgement

The Authors are thankful to Hem Deep Organics Pvt. Ltd mfg of Bulk drugs and intermediates, Ankleshwar. Dist. Bharuch, Gujarat, India., for the gift sample of Furosemide.

References

1. Florey, Analytical Profile Of Drug substances,18,Edited by-Klaus Florey,153-193.
2. British pharmacopeia, Vol-I-II, Euro monographs 0391.
3. The Merck Index., An Encyclopedia of Chemicals, Drugs and Biologicals, 13th edition, Merck & Co., Inc., NJ, 3961.Ganesh C.
4. Ganesh Chaulang.,Formulation and Evaluation of Solid Dispersions of Furosemide in Sodium Starch Glycolate, Tropical Journal of Pharmaceutical Research, February 2009, 8 (1),43-51.
5. Shah Jigar, Vasanti S, Anroop.B, Enhancement of dissolution rate of Valdecoxib by Solid dispersions technique with PVP K 30 & PEG 4000: preparation and in vitro evaluation, J Incl Phenom Macrocycl Chem.,2009, 63,69-75.
6. Kumar Narendra, Development, Characterization, and Solubility Study of Solid Dispersion of Terbinafine Hydrochloride, International Journal of Pharmaceutical Sciences and Nanotechnology, 2008,1(2),171-176.
7. Serajuddin Abu T.M, Solid dispersion of Poorly Water Soluble Drugs: Early Promises, Subsequent Problems, and recent Breakthroughs, Journal of Pharmaceutical Sciences,1999,88(10), 1058-1066.
8. Aulton M.E., 'Pharmaceutics- The science of Dosage form design', second edition,Churchill Livingstone, 469-471.
9. The USP NF 2004, Asian Edition, United States pharmacopeial convention Inc Rockville, MD 20853.
10. Ilse Weuts, Dieter Kempen, Physical stability of the amorphous state of Loperamide and two fragment molecules in solid dispersions with the polymers PVP-K30 and PVP-VA64, European Journal of Pharmaceutical Sciences,2005, 25, 313–320.
11. Kumar N, Development, characterization, and solubility study of solid dispersion of terbinafine hydrochloride by solvent evaporation method, Asian journal of Pharmaceutics, 2008,154-158.

12. Srinarong P., 2009,strongly enhanced dissolution rate of fenofibrate solid dispersion tablets by incorporation of superdisintegrants, European Journal of Pharmaceutics and Biopharmaceutics, (2009),73, 154–161.
13. Sammour A. Omaima , Formulation and Evaluation of Mouth Dissolving Tablets Containing Rofecoxib Solid Dispersion,AAPS PharmaTech.,2006, 7(2),E1-E9.
14. Bikiaris Dimitrios, Z George, Physicochemical studies on Solid dispersion poorly water soluble drugs, evaluation of capabilities and limitations of thermal analysis technique, Thermochimia acta,2005,439,58-67.
15. Remeth D. In-vitroAbsorption Studies of Mucoadhesive Tablets of Acyclovir.Indian Journa lof Pharmaceutical Education and Research.Apr-Jun, 2010,183-188.

*****