ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Formulation and Evaluation of Piroxicam Solid Dispersion with Suitable Carrier

Varma V*[1], C Sowmya[1], Tabasum SG

Department of Pharmaceutics, Raghavendra Institute Of Pharmaceutical Education And Research, K R Palli Cross, Near SK University, Anantapur Dt, A.P., India- 515 721.

ABSTRACT

Piroxicam is a long acting potent NSAID with inflammatory potency and good analgesic-antipyretic action. It is a reversible inhibitor of COX lowers PG concentration in synovial fluid and inhibits platet aggregation prolonging bleeding time. In addition it decreases to IgM rehumatoid factor and leucocyte chemotaxis. Thua it can inhibit inflammation in diverse ways. Solid dispersion were by preliminary solubility analysis was carried out for the selection of carriers and solid dispersion was prepared with PEG 4000 PEG 6000 and mannitol. To increase the solubility of drug solid dispersion was prepared. These solid dispersions were analysed for the solubility and *Invitro* dissolution profile, solid dispersion of drug with PEG 6000 had shown enhanced solubility with improved dissolution rate. The FTIR and DSC studies revealed that there is no interaction between drug and carriers. Solid dispersion prepared with PEG 4000 shows the presence of amorphous form confirmed by the characterization study like SEM sudies. The study also shows the dissolution rate of Piroxicam can be enhanced to considerable extent by solid dispersion technique with PEG.

Keywords: Piroxicam, Solid dispersion, PEG 4000, PEG 6000 and Mannitol.

Corresponding author

ISSN: 0975-8585

INTRODUCTION

Chiou and Riegelman 1971 defined the term solid dispersion as "A dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by the melting (fusion), solvent or melting-solvent method." Dispersions obtained through the fusion process are often called melts, and those obtained by the solvent method are frequently referred to as co-precipitates or co-evaporates [1].

HISTORICAL BACKGROUND:

In 1961, a unique approach of solid dispersion to reduce the particle size and increase rates of dissolution and absorption was first demonstrated by Sekiguchi they proposed the formation of a eutectic mixture of a poorly soluble drug such as sulfathiazole with a physiologically inert, easily soluble carrier such as urea. The eutectic mixture was prepared by melting the physical mixture of the drug and the carrier, followed by a rapid solidification process. Upon exposure to aqueous fluids, the active drug was expected to be released into the fluids as fine, dispersed particles because of the fine dispersion of the drug in the solid eutectic mixture and the rapid dissolution of the soluble matrix [2].

Levy and Kanig subsequently noted the possibility of using a solid solution approach in which a drug is dispersed molecularly in a soluble carrier. In a series of reports in 1965-66, Goldberg et al presented a detailed experimental and theoretical discussion of advantages of solid solution over the eutectic mixture.

In 1965, Tachibana and Nakamaru reported a novel method for preparing aqueous colloidal dispersions of β-carotene by using water-soluble polymers such as polyvinyl pyrrolidone. They dissolved the drug and the polymer carrier in a common solvent and then evaporated the solvent completely. A colloidal dispersion was obtained when the coprecipitate was exposed to water.

In 1966, Mayersohn and Gibaldi demonstrated that the dissolution rate of griseofulvin could be markedly enhanced when dispersed in polyvinyl pyrrolidone by the same solvent method.

Chiou and Riegelman recently advocated the application of glass solution to increase dissolution rates. They used PEG 6000 as a dispersion carrier. It is believed that this relatively new field of pharmaceutical technique and principles will play an important role in increasing dissolution, absorption and therapeutic efficacy of drugs in future dosage forms. Therefore, a thorough understanding of its fast release principles, methods of preparation, selection of suitable carriers, determination of physical properties, limitations and disadvantages will be essential in the practical and effective application of this approach. In addition to absorption enhancement, the solid dispersion technique may have numerous pharmaceutical applications which remain to be further explored [3]. It is possible that such a technique can be used to

obtain a homogeneous distribution of a small amount of drug at solid state, to stabilize unstable drugs, to dispense liquid or gaseous compounds, to formulate a fast release priming dose in a sustained release dosage form, and to formulate sustained release regimens of soluble drugs by using poorly soluble or insoluble carriers

Types of solid dispersions [4]:

a) **Simple eutectic mixture**: An eutectic mixture of a sparingly water soluble drug and a highly water soluble carrier may be regarded thermodynamically as an intimately blended physical mixture of its two crystalline component. The increase in surface area is mainly responsible for increased rate of dissolution. This led to a conclusion that the increase in dissolution was mainly due to decreased particle size.

b) **Solid solutions**: Solid solutions consist of a solid solute dissolved in a solid solvent. A mixed crystal is formed because the two components crystallize together in a homogenous one-phase system. Hence, this system would be expected to yield much higher rates of dissolution than simple eutectic systems.

c) **Glass solution of suspension:** A glass solution is a homogenous system in which a glassy or a vitreous of the carrier solubilizer drug molecules in its matrix. PVP dissolved in organic solvents undergoes a transition to a glassy state upon evaporation of the solvent.

d) **Compound or complex formation:** This system is characterized by complexation of two components in a binary system during solid dispersion preparation. The availability of the drug from the complex is dependent on the solubility dissociation constant and the intrinsic absorption rate of the complex.

The different ways of increasing the rate of absorption or total bioavailability of drugs are: -

1. Micronization
2. Use of soluble salt
3. Use of minuscular form of drug adsorbed on insoluble adsorbents
4. Use of surfactants
5. Use of polymorphs
6. Use of hydrates or solvates, and
7. Molecular complexation

By micronization, reduction in the therapeutic dose of griseofulvin to the extent of 50% and it also produced a constant blood-level.

In 1961, a new approach of solid-dispersion was devised and demonstrated by Sekiguchi and Obi. This provided a new approach to particle size reduction and increased rates of dissolution. Sekiguchi and Obi proposed the formation of a eutectic mixture of a poorly soluble drug such as Sulphathiazole with a physiologically inert, easily soluble carrier such as Urea [5].

The method involves the preparation of a microcrystalline or molecular dispersion of the drug in a solid-matrix of water-soluble physiologically inert carrier like urea. The melted sulphathiazole and urea was followed by rapid solidification. The fine dispersion of the drug in the solid eutectic mixture and the rapid dissolution of the soluble matrix promoted a fast release of the drug into the surrounding fluid. It presented a detailed experimental and theoretical discussion of the advantages of the solid solution over the eutectic mixture.

Co-precipitates and melts are solid dispersions that provide a means of reducing particle size to the molecular level. Sekiguchi and Obi, 1961 first introduced the concept of using solid dispersions to improve bioavailability of poorly water-soluble drugs. They demonstrated that the eutectic of sulphathiazole and physiologically inert water-soluble carrier urea exhibited higher absorption and excretion after oral administration than sulfathiazole alone. Recent work on dispersions has been extended to the development of sustained-release preparations [6].

Methods of preparatioN

The two basic procedures used to prepare solid dispersions are the fusion and co solvent techniques. Modifications of these methods and combinations of them have also been used.

(a) Melting or fusion method

Sekiguchi and Obi, 1961 first reported this method. A physical mixture of an active agent and a water-soluble carrier is heated until it is melted. The melt is solidified rapidly in an ice bath under rigorous stirring, pulverized, and then sieved. Rapid congealing is desirable because it results in super saturation of drug as a result of entrapment of solute molecules in the solvent matrix by instantaneous solidification. The solidification process can be achieved on stainless steel plates attached to a cooling system to favor rapid heat loss [7]. Spray congealing from a modified spray drier onto a cold metal surface has also been used. Products from this process can be obtained in pellet form without the necessity of a grinding step that may alter crystalline modification.

Two advantages of the melt method are its simplicity and its economy, as no solvents are involved. However, the method may not be suitable if the drug or the carrier is unstable at the fusion temperature or evaporates at high temperatures. Succinic acid, for example, used as a carrier for griseofulvin is quite volatile and partially decomposes by dehydration near its melting point. Such problems can be avoided by melting in a sealed container, under vacuum or under an inert gas such as nitrogen. By proper selection of carrier system and composition, the melting point of a binary system can be much lower than the melting point of either of the components.

Other disadvantages of this method may include the tacky and intractable nature of the resulting solidified melt and irregular crystallization owing to the presence of a miscibility gap on the phase diagram for a given drug-carrier system.

(b) Solvent method

Nomura, et al., 1996 first used this method to prepare a solid dispersion of β-carotene in PVP by using chloroform as a cosolvent. Solutions or mixed crystals could be prepared by dissolving a physical mixture of two solid components in a common solvent followed by evaporation of the solvent. The solvent is usually removed by evaporation under reduced pressure at varying temperatures. The choice of solvent and its removal rate are critical to the quality of the dispersion [8].

The freeze-drying process has been used to prepare dispersions of ketoprofen and dicumarol in PVP from their ammoniacal solutions (Margarit, et al., 1994). The major advantage of the solvent method is that thermal decomposition of drugs and carriers associated with the fusion method can be avoided. The disadvantages include the higher cost of preparation the use of large quantities of solvent and the difficulty in complete removal of solvent, the possible adverse effect of residual solvent, the selection of a common volatile solvent, the difficulty of reproducing crystal forms, and the inability to attain a super saturation of the solute in the solid system unless the system goes through a highly viscous phase [9].

(c) Melting solvent method

It has been found that 5-10% (w/w) of liquid compound could be incorporated into PEG 6000 without significant loss of its solid property. Thus solid dispersions can be prepared by first dissolving a drug in a suitable liquid solvent and then incorporating the solution directly into the melt of polyethylene glycol (obtained below 70^0C) without removing the solvent. This unique method combines the advantages of both the melting and solvent methods but it is limited only to drugs with a low therapeutic dose.

(d) Solvent deposition method

In this method, a water insoluble drug is dissolved and equilibrated in an organic solvent, and then deposited onto excipients (insoluble in the organic solvent) by constant evaporation of the organic solvent at room temperature and atmospheric pressure/under vacuum. From various studies, it has been established that during the evaporation of solvent, drug undergoes molecular micronization and recrystallizes as a 'minuscular form'.

MATERIALS AND METHODS

Piroxicam was obtained as gift sample from Halmack pharmaceuticals, Hyderabad. PEG 6000, PEG 4000 & Mannitol were obtained from ONTOP Pharmaceuticals, Bangalore. All other chemicals and solvents used for analytical grade only.

Preparation of Solid dispersion [10]:

The preparation of Piroxicam solid dispersions using different concentration of PEG 6000, PEG 4000 & Mannitol by using the Physical Mixture & Fusion methods.

Preparation by physical mixture method

The ratio of drug: mixed excipient system was kept constant (1:1 w/w) in all formulations. Physical mixtures of Piroxicam with mixed excipient system including PEG 6000, PEG 4000 & Mannitol were prepared by mixing accurately the weighed amount of drug and carrier with the help of a spatula in a glass mortar [11].

Fusion method

The melting or fusion method involves the preparation of physical mixture of a drug and a water-soluble carrier and heating it directly until it method mixture is then solidified rapidly in an ice –bath under vigorous stirring. The final solid mass is crushed, pulverized and sieved. appropriately this has undergone many modifications in pouring the homogenous melt in the form of a thin layer onto a ferrite plate or a stainless steel plate and cooled by flowing air or water on the opposite side of the plate in addition, a super-saturation of a solute or drug in a system can often be obtained by quenching the melt rapidly from a high temperature. Under conditions, the solute molecule is arrested in the solvent mixture by the instantaneous solidification process [12]. The quenching technique gives a much final dispersion of crystals when used for simple eutetic mixtures.

Table:1 Formulation of Piroxicam Solid dispersion

SI.No	Formulation Codes	Carrier	Drug: Carrier	Method
1.	SDP 1	PEG 4000	1:1	Physical Method
			1:2	Fusion method
2.	SDP 2	PEG 6000	1:1	Physical Method
			1:2	Fusion method
3	SDP 3	Manniitol	1:1	Physical Method
			1:2	Fusion method

Preliminary solubility studies of Piroxicam

Solubility measurements of Atorvastatin were performed according to a published method (Higuchi and Connors, 1965). An excess amount of Piroxicam was added to 25ml of aqueous solution of water soluble carriers like PEG 4000, PEG 6000 & Mannitol in the various ratios such as 1:1, 1:2 (Physical & Fusion method) in screw capped bottles [13]. Samples were shaken for the 24 hours at room temperature. Subsequently, the suspensions were filtered through a Whatman filter paper no 1. Filtered solution diluted properly with methanol. The diluted solution analyzed for the Atorvastatin in UV 358nm.

Evaluation of solid dispersion

Solid dispersions obtained from the above methods were screened for their solubility [14]. The solid dispersion showing good solubility were further studied for drug content, in vitro release studies, FTIR & DSC study.

Drug content [14]

The amount of drug present in a 10 mg equivalent amount of solid dispersion was determined by, dissolving the powder mixture in 10 ml of methanol and suitably diluted with methanol and UV absorbance was measured at 358 nm. Drug concentration was determined from standard graph.

In vitro release studies

In vitro dissolution studies were performed for selected solid dispersion. The following conditions were maintained for the dissolution process:

Instrument:	Electro lab- USP Dissolution test apparatus.
Apparatus:	Paddle type.
Temperature:	37±0.10C
RPM:	75
Dissolution medium:	Distilled water.
Volume of medium:	500 ml.
Sampling intervals:	Every 30 min up to 4 hour
Sample volume:	5 ml withdrawn and replaced with 5 ml of distilled water.

Characterization of solid dispersions of Piroxicam

Differential Scanning Calorimetry (DSC) Analysis

DSC scans of the powdered samples Piroxicam, PEG 6000, PEG 4000 & Mannitol were recorded using DSC- Shimadzu 60 with TDA trend line software. All samples were weighed (8-10 mg) and heated at a scanning rate of 20°C/min under dry air flow (100 ml/min) between 50 and 300°C. Aluminum pans and lids were used for all samples.

Infrared (IR) Spectroscopic Analysis [15]

Fourier–transform infrared (FTIR) spectra of moisture free powdered samples were obtained using a spectrophotometer (FTIR-8300, Shimadzu Co., Kyoto, Japan) by potassium bromide (KBr) pellet method (2 mg sample in 200 mg KBr). The scanning range was 750–4000 cm^{-1} and the resolution was 1 cm^{-1}.

ISSN: 0975-8585

Preparation of Solid dispersion

The preparation of Piroxicam solid dispersions using different concentration of PEG 6000, PEG 4000 & Mannitol by using the Physical Mixture & Fusion methods [16]. Batches of solid dispersions of Piroxicam were prepared using factorial design as described in methodology

- Preparation by physical mixture method
- Fusion method

Table:2 Physical Appearance of Piroxicam Solid Dispersions

Method	Physical properties of solid dispersions	
	Colour	Appearance
Physical mixture	White	Fine powder
Fusion method	White	Fine powder

Preliminary solubility studies of Piroxicam

The preliminary solubility of Piroxicam From this physical mixtures & Fusion method of PEG 4000, PEG 6000 & Mannitol, containg different ratio of 1:1, 1:2 for the preparation of the solid dispersion. After preparation of solid dispersion solubility analysis were carried out this is compared with physical mixtures & Fusion method. Drug content of the formulation found to be are in case of PEG 4000 (1:1) carries 0.21mg/ml (1:2) 0.24 mg/ml, PEG 6000 (1:1) 0.23 mg/ml (1:2) 0.26, Mannitol (1:1) 0.25 mg/ml (1:2) 0.27 mg/ml.

Table: 3 Preliminary Solubility (µg/ml) of Piroxicam

Sl.No.	Carrier (Drug: Carrier)	Solubility mg/ml
1	Piroxicam + PEG 4000 (1:1)	0.21
	Piroxicam + PEG 4000 (1:2)	0.24
2	Piroxicam + PEG 6000 (1:1)	0.23
	Piroxicam + PEG 6000 (1:2)	0.26
3	Piroxicam + Mannitol (1:1)	0.25
	Piroxicam + Mannitol (1:2)	0.27

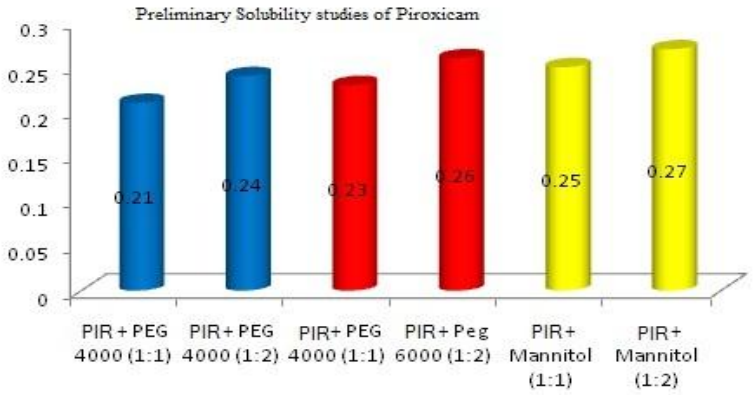

Figure 1 Preliminary solubility studies of Piroxicam

ISSN: 0975-8585

In Vitro drug dissolution studies

For understanding the mechanism of drug release rate kinetics of the drug from dosage forms, the *invitro* drug dissolution data [17]. The % drug release with data to various kinetic models for different Solid dispersion formulations.

Results of *In Vitro* release of Piroxicam from solid dispersion systems of various batches prepared by physical mixture and fusion method.

Name of the drug	Piroxicam
Loading dose in mg	100
Total No. of readings including zero-time reading	7
Dissolution medium Phosphate buffer	pH 7.4
RPM	50
Volume of dissolution medium (ml)	900
Volume of sample removed (ml)	5

Table:4 Cumulative Percentage drug Release of Piroxicam from Solid Dispersions

Sl.No	Time	% Cumulative drug Release					
		PEG 4000 1:1 (PM)	PEG 4000 1:2 (FM)	PEG 6000 1:1 (PM)	PEG 6000 1:2 (FM)	Mannitol 1:1 (PM)	Mannitol 1:2 (FM)
1	10	4.92	10.78	11.05	15.7	8.12	3.12
2	20	11.08	18.46	19.72	23.37	17.35	10.07
3	30	17.27	25.93	30.81	41.92	24.82	16.21
4	40	24.69	34.62	39.52	50.60	33.82	23.71
5	50	40.71	49.46	53.1	70.40	48.35	39.60
6	60	55.59	65.53	70.46	85.34	64.42	54.48

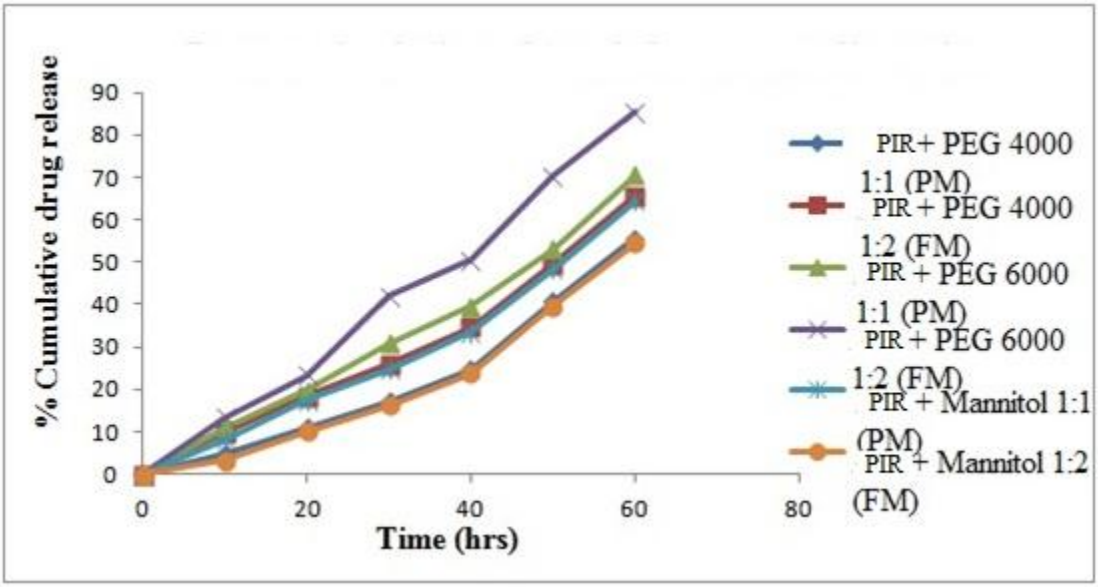

Figure: 2 *Invitro* Dissolution of Piroxicam Solid Dispersion

ISSN: 0975-8585

Fourier transforms Infrared (FTIR) Spectroscopic Analysis

The IR spectrum of the pure Piroxicam sample recorded by FTIR spectrometer is shown in Figure 11. This was compared with standard functional group frequencies of Piroxicam as shown in Table 5.

From FTIR study, the characteristic peaks of drug such as of pyridin-2-ylamino stretch Piroxicam (3340cm^{-1}), PEG 6000(3000cm^{-1}), PEG 4000(3180CM^{-1}), Mannitol (3000cm^{-1}). N-H Stretch for the pure drug Piroxicam(3260 cm^{-1}), PEG 6000(1860cm^{-1}), PEG 4000 (2600cm^{-1}), Mannitol (2000cm^{-1}). Oxa acetic acid Stretch the pure drug Piroxicam (1665 cm^{-1}), PEG 6000 (1250 cm^{-1}), PEG 4000(1760cm-1), Mannitol(1760cm^{-1}). Acetyl group the pure drug Piroxicam methyl (1318cm^{-1}), PEG 6000 (1000 cm^{-1}), PEG 4000 (1250 cm^{-1}), Mannitol (1760 cm^{-1}). For Solid dispersion all peaks which have been obtained for the pure drug were available at same wave length for Remaining peaks also either shifted or replaced in the IR spectrum of formulation.

Table 5 . IR Interpretations for Pure drug Piroxicam, PEG 6000, PEG 4000 and Mannitol

Funtional groups	Pure drug Piroxicam	PEG 6000	PEG 4000	Mannitol
pyridin-2-ylamino stretch	3340cm^{-1}	3000 cm^{-1}	3180cm^{-1}	3000 cm^{-1}
N-H Stretch	3260 cm^{-1}	1860 cm^{-1}	2600 cm^{-1}	2000 cm^{-1}
Oxa acetic acid Stretch	1665 cm^{-1}	1250 cm^{-1}	1760 cm^{-1}	1760 cm^{-1}
Methyl group	1318 cm^{-1}	1000 cm^{-1}	1250 cm^{-1}	1270 cm^{-1}

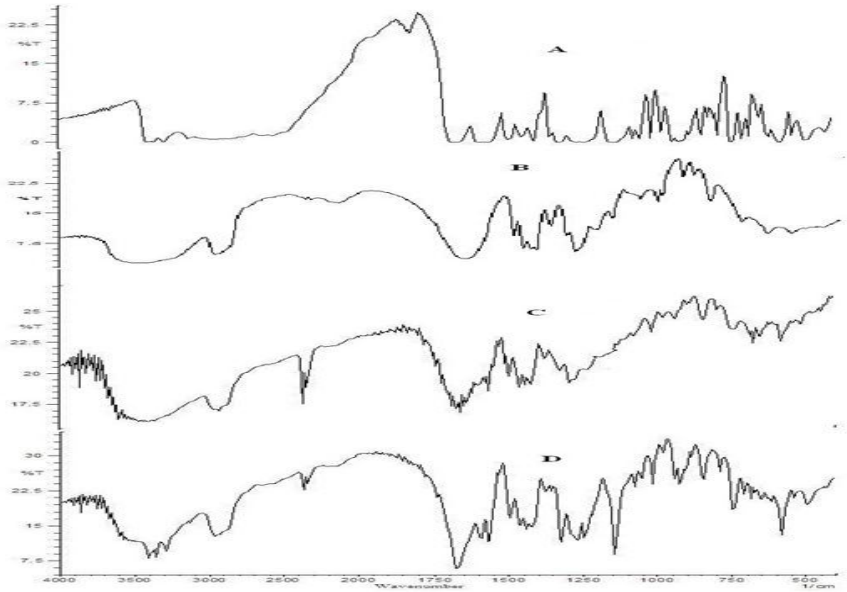

Figure: 3 11FTIR Spectra of a) Piroxicam b) PEG 4000 c) PEG 6000 d) Mannitol

ISSN: 0975-8585

Differential Scanning Calorimetry (DSC) Analysis

The pure drug Piroxicam shown as an endothermic peak at 240 ^{o}C. The peak neither is nor shifted in the case of DSC of the Solid disersion formulation containing PEG 6000, PEG 4000 & Mannitol. The DSC of physical mixture of the PEG 6000 as showed an endothermic peak at 110 ^{o}C & Exothermic peak it shows linear position [18]. The DSC of PEG 4000 showed an endothermic peak 110^{o}C. The DSC of Mannitol shows 100^{o}C which shown endothermic there is no incompatibility exist in the formulation. The IR spectra as shown in Figure 4.

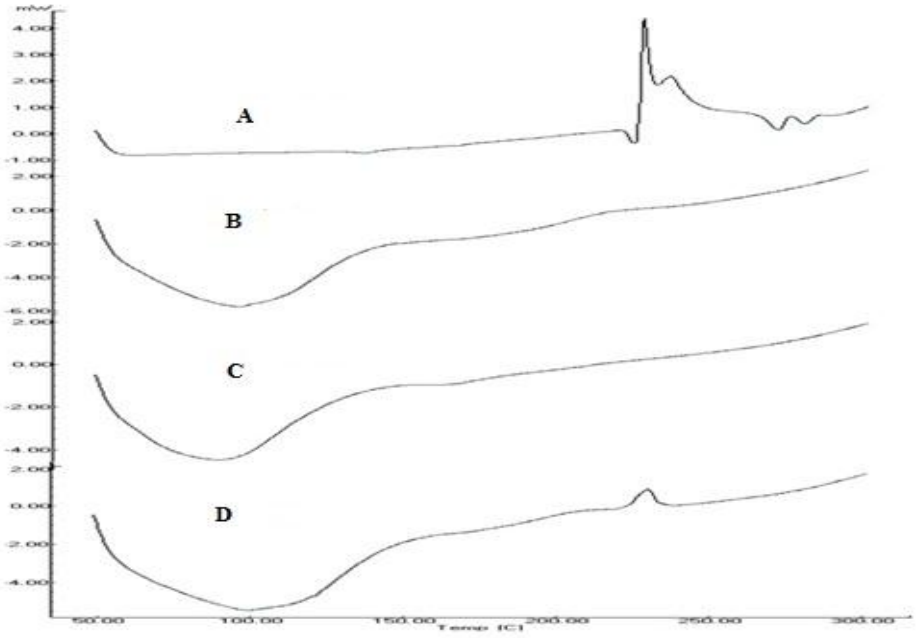

Figure:4 DSC Spectra of a) Piroxicam b) PEG 4000 c) PEG 6000 d) Mannitol

CONCLUSION

Finally it could be concluded that Solid dispersion of Piroxicam using hydrophilic polymers would improved the aqueous solubility, dissolution rate and thereby enhancing its systemic availability. In present study solid dispersion prepared with PEG 6000 shows the presence of amorphous form confirmed by the characterization study. Solid dispersion preliminary solubility analysis was carried out for the selection of carriers and solid dispersion was prepared with PEG- 6000, PEG 4000 and Mannitol, The best formulation for is PEG 6000 1:1, 1:2 (Physical & Fusion method). These solid dispersions were analysed for the solubility and Invitro dissolution profile, solid dispersion of drug with PEG 6000 had shown enhanced solubility with improved dissolution rate. From IR & DSC spectroscopy concluded that the there is no compatability studies interaction between Piroxicam and carriers.

REFERENCES

[1] Chiou W, Riegelman S. J Pharm Sci 2006; 60 (10): 1569-1571.

[2] Chiou WL, Riegalman S. J Pharm Sci 1971; 60: 1281–1302.
[3] Christian L, Jennifer D. Eur J Pharm Biopharm 2000; 50: 47-60.
[4] Craig DQM. Int J Pharma 2002; 231: 131-144.
[5] James S, James CB. Encyclopedia of Pharmaceutical Technology 2000; 3: 337.
[6] Leuner C, Dressman J. Eur J Pharm Biopharm 2000; 50: 47-60.
[7] Melgardt MV, Dale EW, Jakkie G, Amol K. Int J Pharma 1986; 163: 219–224.
[8] Muller RH, Jacobs C, Kayser O. Adv Drug Deliv Rev 2001; 54: 131-155.
[9] Nomura S, Kai T, Akiyama Y, Sato M. Chem Pharm Bull 1996; 44: 568–571.
[10] Sanghavi NM, Choudhari KB, Matharu RS, Viswanathan L. Drug Deve Ind Pharm 1993; 19: 701-712.
[11] Serajuddin ATM. J Pharm Sci 1999; 88: 1058-1066.
[12] Teresa MM, Victoria MM, Gloria ES. Farmaco 2002; 57: 723-727.
[13] Serajuddin ATM. J Pharm Sci 2000; 88 (10): 1058-1066.
[14] Bruckert E, Davidoff P, Grimaldi A. J Am Med Assoc 1990; 263(1):35-36.
[15] Bonnie KY, Anne B, Sotirios T et al. J Am Coll Cardiol 2008; 51(17): 1653-1662.
[16] Shewale BD, Sapkal NP, Raut NA et al. Indian J Pharm Sci 2008; 70(2): 255–257.
[17] Subrahmanyam CVS, Text Book of Physical Pharmaceutics. 2nd ed. New Delhi, Vallabh Prakashan; 2000, pp. 358.
[18] Michael SH, Jinxiu L, Yevgeniy I et al. J Bone Miner Res 2008; 23(10):1672–1679.