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Formulation, Optimization, and Characterization of Solid Dispersion of Piroxicam by Mixed Solvency Technique

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ABSTRACT

The present research study aims to explore the possibility of employing mixed solvency techniques in the formulation of a poorly water-soluble drug. In the present study, practically water-insoluble drugs, piroxicam is solubilized by employing the combination of physiologically compatible water-soluble additives (solubilizers) to attempt its immediate-release formulations. Solid dispersion containing drug: solubilizer in ratio 1:8 showed a faster dissolution rate than piroxicam pure drug, physical mixture. From detailed studies, it can be predicted that the approach of mixed solvency is novel, safe, cost-effective and user-friendly. It also eliminates the problem of toxicity associated with a high concentration of water-soluble solubilizers. So, it may be employed in dosage form development of drugs where the fast onset of action desired. It may also enhance the bioavailability associated with the poor dissolution of the drug.

INTRODUCTION:

Dissolution is the process by which a solid solute enters in solution. In the pharmaceutical industry, it may be defined as the amount of drug substance that goes into solution per unit time under standardized conditions of liquid/solid interface, temperature and solvent composition.

Cosolvents are defined as water-miscible organic solvents that are used in liquid drug formulations to increase the solubility of poorly water-soluble substances or to enhance the chemical stability of a drug. Cosolvency, then, refers to the technique of using cosolvents for the stated purposes; it is also commonly referred to as solvent blending. Cosolvency has been used as an approach for preparing liquid drug preparations throughout the history of drug formulation. In many cases, cosolvency can increase the solubility of a non-polar drug up to several orders of magnitude above the aqueous solubility. This would be significant, for example, in a formulation problem where it might be necessary to increase the solubility of a drug 500-fold or more. The use of cosolvents to prepare solution formulations of non-polar drugs is a simple and potentially effective way to achieve high concentrations of the drug.

Mixed Solvency concept was proposed by Maheshwari and proved that water-soluble substances whether liquids, solids or gases may enhance the solubility of poorly soluble drugs. He has carried out solubility studies on poorly-water soluble drug salicylic acid (as model drug). Solubility studies were carried in the solutions containing hydrotropic agents (urea and sodium citrate), cosolvents (glycerin, propylene glycol, PEG 300 and PEG 400) and water-soluble solids (PEG 4000 and PEG 6000) individually as well as in 10 randomly prepared blends keeping total concentration constant i.e. 40 %. Results showed that seven out of ten blends produced a synergistic effect on solubility enhancement.

Solid Dispersions term refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or crystalline particles. Solid dispersions are defined as the dispersion of one or more active ingredients in an inert carrier or matrix prepared by melting, solvent or melting solvent method. The physical state of the drug in the solid dispersions is often transformed from crystalline to amorphous form and the dissolution surface increases because of particle size reduction. Because of promises in the bioavailability enhancement of poorly water-

soluble drugs, solid dispersion has become one of the most active areas of research in the pharmaceutical field.

Characterization of Solid Dispersions:

- Modulated temperature differential scanning calorimetry
- Dissolution testing
- Drug content determination
- Phase solubility study
- Thermal analysis
- Powdered X-ray diffraction
- Infrared spectroscopy
- Stability study

NEED AND OBJECTIVES OF WORK

The need for work

The solubility of a drug is an important molecular property that mainly influences the extent of oral bioavailability. Poor aqueous solubility is a very challenging problem in drug formulation development. Due to poor aqueous solubility, many drug candidates, become unsuccessful to reach the market although exhibiting potential pharmacodynamic properties. It is very useful to find appropriate formulation approaches to improve aqueous solubility and thus bioavailability of poorly soluble drugs.

Piroxicam is a cyclooxygenase inhibiting, non-steroidal anti-inflammatory agent (NSAID) that is well established in treating rheumatoid arthritis and osteoarthritis and used for musculoskeletal disorders, dysmenorrhea, and postoperative pain. piroxicam drug exhibits low bioavailability related to its poor water solubility. Piroxicam is a B.C.S class II compound, i.e., water-insoluble, lipophilic, and highly permeable according to Biopharmaceutical Classification System. Therefore, Piroxicam bioavailability can be improved by increasing its solubility.

The estimated bioavailability is greater than 60%; however, the plasma levels do not increase proportionally with the increase in dose. The calculated biopharmaceutical parameters suggested that piroxicam has an absorbable dose of 10 & 20 mg, which is far below the lowest dose of the drug. Also the volume of aqueous medium required to dissolve the highest dose, thus theoretically piroxicam exhibits a solubility limited bioavailability and it would be advantageous to increase the solubility of such molecules.

Objectives of work

- The present study aims to prepare the solid dispersion of Piroxicam by the mixed solvency concept.
- To characterize and optimize solid dispersion.
- To study enhance the dissolution rate of the drug.

MATERIALS AND METHODS:

Table No. 1: List of Material Used

Sr. No.	Ingredient	Suppliers
1	Piroxicam	Mesha Pharma Ltd. Mumbai
2	Hydroxypropyl beta cyclodextrin	Glenmark Ltd. Mumbai
3	Niacinamide	Morden Lab Ltd. Indore
4	Sodium benzoate	S D fine chemicals, Mumbai
5	Sodium citrate	S D fine chemicals, Mumbai
6	PEG 400	S D fine chemicals, Mumbai
7	PEG 8000	S D fine chemicals, Mumbai
8	PVP K 30	S D fine chemicals, Mumbai
9	HCL	S D fine chemicals, Mumbai

METHODS

Steps implemented in the presented research are as follows:

A. DRUG CHARACTERISATION:

Drug characterization was done by different physical as well as instrumental methods. Physical determinations include Organoleptic properties, Melting point determination. UV absorption in different solvents like 0.1 N HCL, Distilled Water and Simulated Saliva Fluid was studied. Also sophisticated instrumental characterization with FTIR, XRD and DSC thermogram was made.

B. PREPARATION OF CALIBRATION CURVES:

Calibration curves of piroxicam in distilled water, 0.1N HCl and in simulated saliva fluid (pH 6.8) were prepared.

C. DETERMINATION OF SOLUBILITY:

Solubility of piroxicam is determined in the selected solvents, i.e., distilled water, 0.1 N HCl & simulated saliva fluid. Solubility studies in different solvent mediums were carried out by adding an excess amount of drug (piroxicam) in the 10 ml of respective medium and keeping the screw-capped tubes containing these solutions, on a mechanical shaker at room temperature for 12 hrs. so that equilibrium solubility can be achieved. The absorbances of the solutions were measured at 358.6 nm on a double beam UV/Visible spectrophotometer. The amount of drug was quantified from the respective curves.

D. SELECTION OF WATER-SOLUBLE CARRIERS:

All water-soluble substances whether liquids, solids or gases may act as a solubilizer for poorly water-soluble drugs. Therefore for the present investigation, several solubilizing additives from the category hydrotropic agents (sodium benzoate, sodium acetate, sodium citrate, and niacinamide) and water-soluble solids (HP-BCD, PEG 8000 and PVP K 30) were selected. For the selection of appropriate water-soluble additives that have good solubilizing capacities for piroxicam to prepare solid dispersion, the solubility of piroxicam in aqueous solutions of different solubilizing additives, as well as their blends (keeping the concentration constant i.e. 40 %), were measured. An excess amount of piroxicam was added to 5 ml of

these solutions in volumetric flasks and the volumetric flasks were shaken on a mechanical shaker for 12 hrs so that equilibrium solubility can be achieved and solutions were allowed to equilibrate for 24 hrs. Then solutions were centrifuged at 2000 rpm for 5 minutes in a centrifuge and then solutions were filtered through Whatman grade 41 filter. An aliquot was suitably diluted with distilled water and analyzed using a UV spectrophotometer at 358.6 nm against corresponding reagent blanks.

E. DRUG EXCIPIENT COMPATIBILITY STUDIES BY FTIR:

IR spectra of drug, drug, and polymers were obtained FTIR. The FTIR spectra were recorded using the KBr dispersion method in the region of 400-4000 cm-1. Spectra were recorded for pure drug, pure excipients and physical mixture of drug and excipients.

F. PREPARATION OF SOLID DISPERSIONS:

a. Formulation and preparation of solid dispersions of piroxicam by application of Mixed solvency concept:

For the preparation of solid dispersion in1:4 ratio (drug: solubilizers blend) accurately weighed 1.5 gm. sodium benzoate,1.5 gm. HP-BCD and 1 gm. PVP K 30 were taken in a 100 ml beaker and were mixed properly. Then the minimum possible quantity of warm, distilled water sufficient to dissolve the above mixture was added, because the lesser the amount of water lesser will be the time required to evaporate it and chemical stability of drug may not be affected adversely (during removal of water). After the complete dissolution of solubilizers, 1 gm. of piroxicam was dissolved in the above solution and temperature was maintained in the range of 55-60ºC to facilitate the evaporation of water. As evaporation proceeded, the speed of rice bead automatically decreased and it stopped stirring when most of the water was evaporated, thus indicating the formation of solid dispersion (wet). The same procedure was utilized to prepare solid dispersion in the ratio of 1:6, 1:8,1:10 and1:12 using an appropriate quantity of solubilizers.

b. Formulation and preparation of a physical mixture of piroxicam:

For preparing physical mixture in 1:4 ratio, accurately weighed 1 gm of Piroxicam, 1gm of PVP K 30, 1.5 gm sodium benzoate and 1.5 gm of HP-BCD were mixed. After complete

mixing, the powder mass was passed through sieve # 40. The same procedure was utilized to prepare a physical mixture in the ratio of 1:6, 1:8, 1:10, and 1:12.

G. CHARACTERIZATION OF SOLID DISPERSIONS:

a. Determination of drug content in solid dispersion and physical mixtures:

Powder solid dispersion or physical mixture equivalent to 10 mg of piroxicam was accurately weighed and dissolved completely in distilled water in a 100 ml volumetric flask. The concentration of this resulting solution was 100µg/ml. 1 ml of this solution was diluted to 10 ml with distilled water. The solution was analyzed spectrophotometrically at 358.6 nm against corresponding reagent blank and drug contents were determined.

b. Percentage Yield:

The yields of production of solid dispersions of various batches were calculated using the weight of the final product after drying concerning the initial total weight of the drug and polymer used for the preparation of solid dispersions.

c. Micromeritic properties of solid dispersion:

Determination of angle of repose, Carr's index and Hausner's ratio were used to characterize the flow properties of the solid dispersion powder systems. The flowability of a powder is of critical importance in the production of pharmaceutical dosage forms to get a uniform feed as well as the reproducible filling of the capsule, otherwise, high dose variations will occur.

d. Solubility Study:

The apparent solubility of solid dispersions of Piroxicam was determined in distilled water. Each solid dispersion in excess quantity was added to 10 ml of solvent in glass vials with rubber closers. Then the vials were kept on a rotary shaker for 12 h. After shaking, the vials were kept in room temperature equilibrium for 24 h. The solution was then filtered through 41 Whatman filter paper and the filtrate was assayed spectrophotometrically at 358.6 nm.

e. *In-vitro* dissolution rate studies:

Dissolution tests become especially important when dissolution is the rate-limiting step as in the case of B.C.S. class II or B.C.S. class IV drugs. To select the optimum ratio of solid

dispersion, physical mixture, plain drug, and final formulation, dissolution rate studies were performed. The procedure as per BP was followed for *In-vitro* dissolution rate studies. After performing the SD dissolution study, optimized solid dispersion filled in a hard gelatin capsule and performed a dissolution study of this prepared capsule, and compare with the marketed capsule.

f. Fourier transforms IR spectroscopy:

Fourier-transform infrared (FT-IR) spectra were obtained. The samples of physical mixture 1:8 and optimized solid dispersion 1:8 were previously ground and mixed thoroughly with potassium bromide, the FTIR spectra were recorded using the KBr dispersion method in the region of 400-4000 cm^{-1}.

g. Differential Scanning Calorimetry (DSC):

The DSC measurements were performed on a differential scanning calorimeter with a thermal analyzer. All accurately weighed samples of physical mixture 1:8 and optimized solid dispersion 1:8 were placed in sealed aluminum pans, before heating under nitrogen flow (20ml/min) at a scanning rate of 10°C min^{-1} from 20 to 300°C. An empty aluminum pan was used as a reference.

RESULTS AND DISCUSSION

A. DRUG CHARACTERISATION:

a. Organoleptic properties of drug:

Table No. 2: Organoleptic properties of drug

Test	Specification/Limits	Observations
Colour	White or Slightly yellow	Slightly yellow
Odor	Odorless	Odorless
Nature	Crystalline powder	Crystalline powder

b. Melting point:

The melting point of Piroxicam was found to be 197-199^{0}C which complies with that given in the literature i.e. 199-200^{0}C.

c. UV ABSORPTION OF PIROXICAM:

i. In 0.1 N HCl: The drug sample exhibited λmax. at 333.4 nm in 0.1 N HCl, This λmax is the same as reported in the literature.

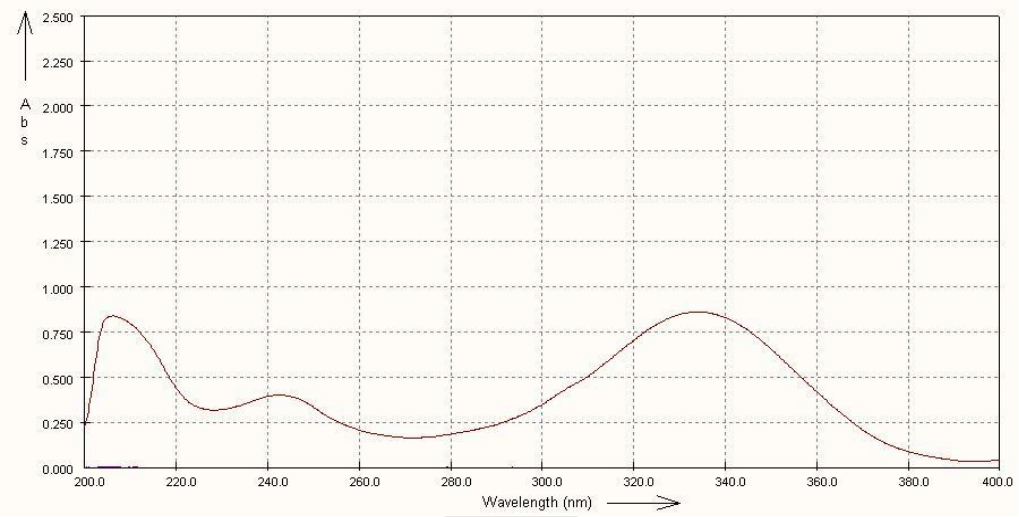

Figure No. 1: UV spectrum of a piroxicam drug sample in 0.1N HCl

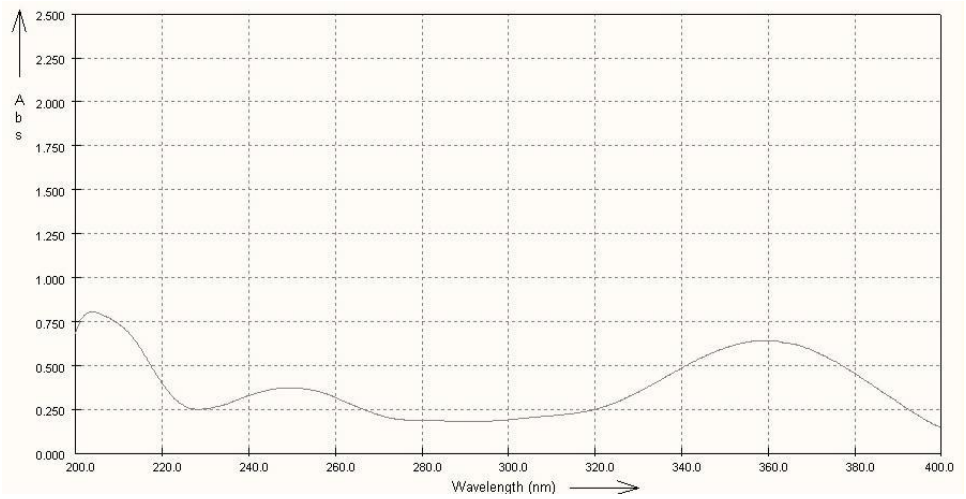

Figure No. 2: UV spectrum of a piroxicam drug sample in distilled water

ii. In Distilled Water: The drug sample exhibited λmax. at 358.6 nm in distilled water, This λmax is the same as reported in the literature.

iii. Simulated Saliva Fluid: The drug sample exhibited λmax. at 358.4 nm in simulated saliva fluid PH 6.8, This λmax is the same as reported in the literature.

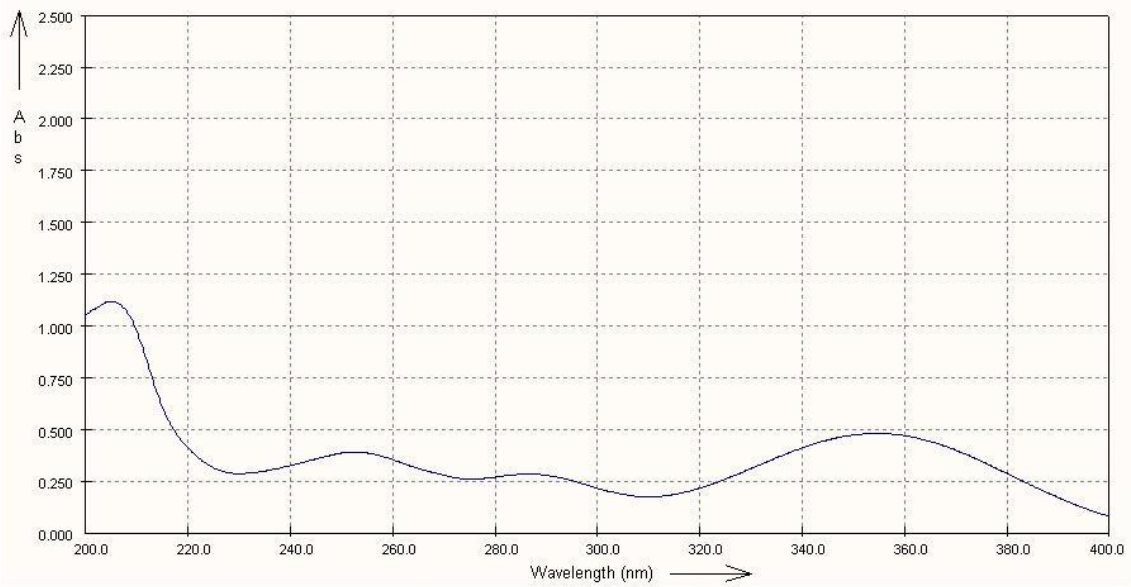

Figure No. 3: The UV spectrum of a piroxicam drug sample in simulated saliva fluid PH 6.8

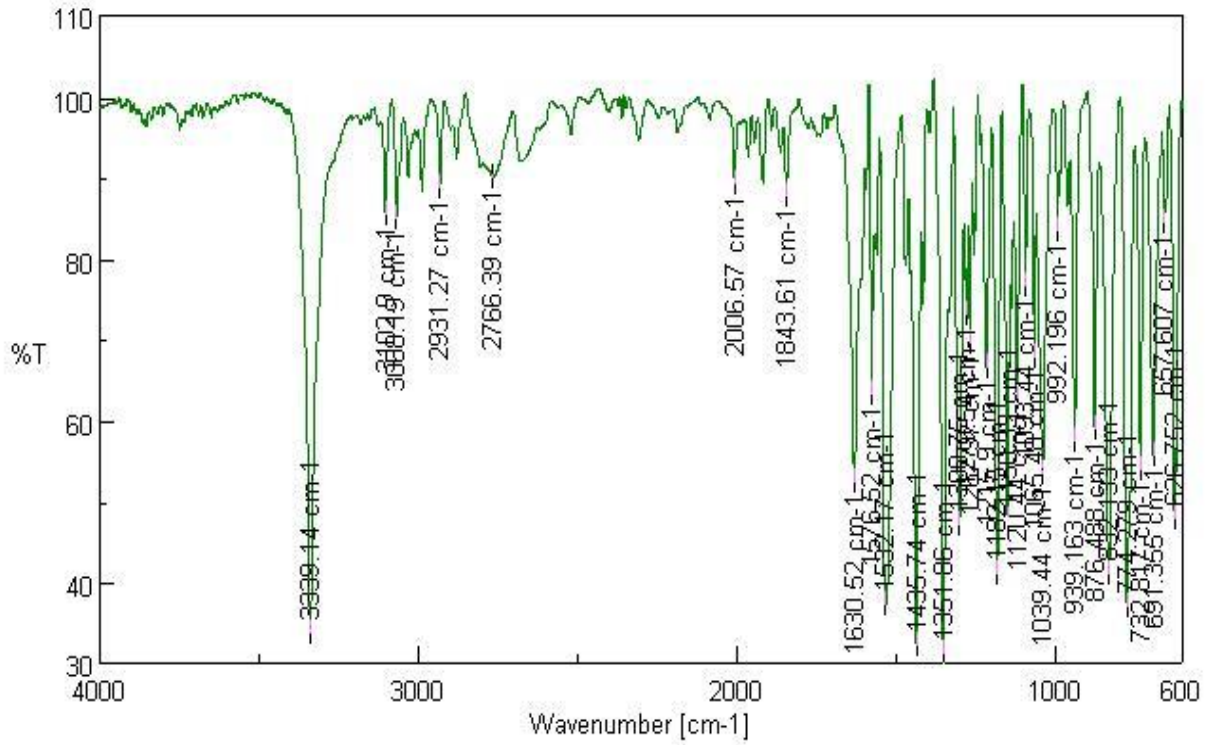

Figure No. 4: FTIR spectrum of piroxicam drug sample

d. FTIR Spectroscopy:

The FTIR spectrum of drug samples was shown identical peaks ranges the same as a reported sample of piroxicam.

Table No. 3: Interpretation of infrared spectrum bands of piroxicam drug sample

Sr. No	Observed Wavenumber (cm^{-1})	Standard Wavenumber (cm^{-1})	Interpretation
1	3339.14	3339	N-H stretching
2	1532.17	1524	C=N ring stretching
3	1300.75	1298	$-SO_2$ Asymmetric stretching
4	1150.33	1147	$-SO_2$ symmetric stretching
5	1576.52	1573	N-H bending
6	691.35	690	C-S Stretching
7	774.27	770	Ortho disubstituted benzene ring

e. X-ray powder diffraction (XRD):

X-ray diffraction of piroxicam displayed four major peaks shows at diffraction angles (2θ) 13.10°, 13.40°, 18.50°, 22.10°, and 28.90° showing a typical crystalline pattern.

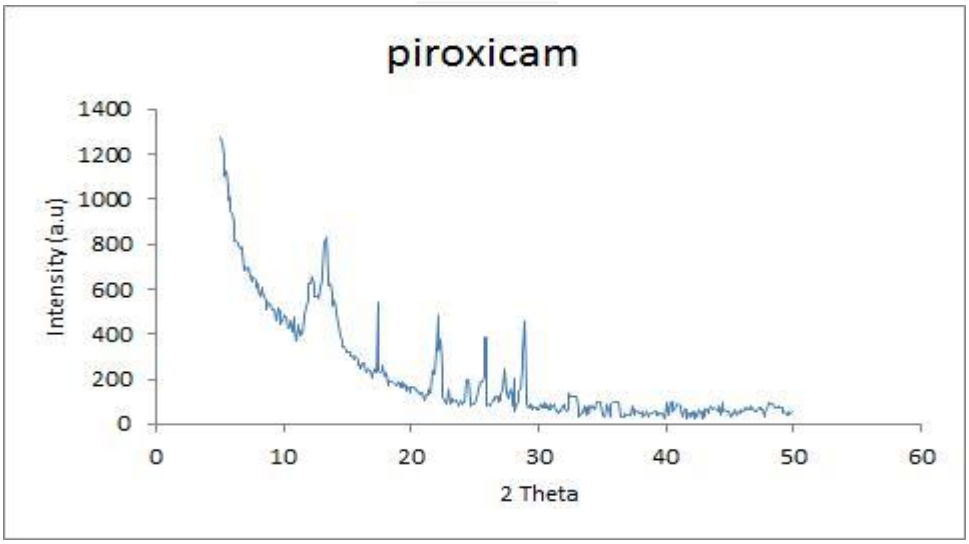

Figure No. 5: XRD of piroxicam drug sample

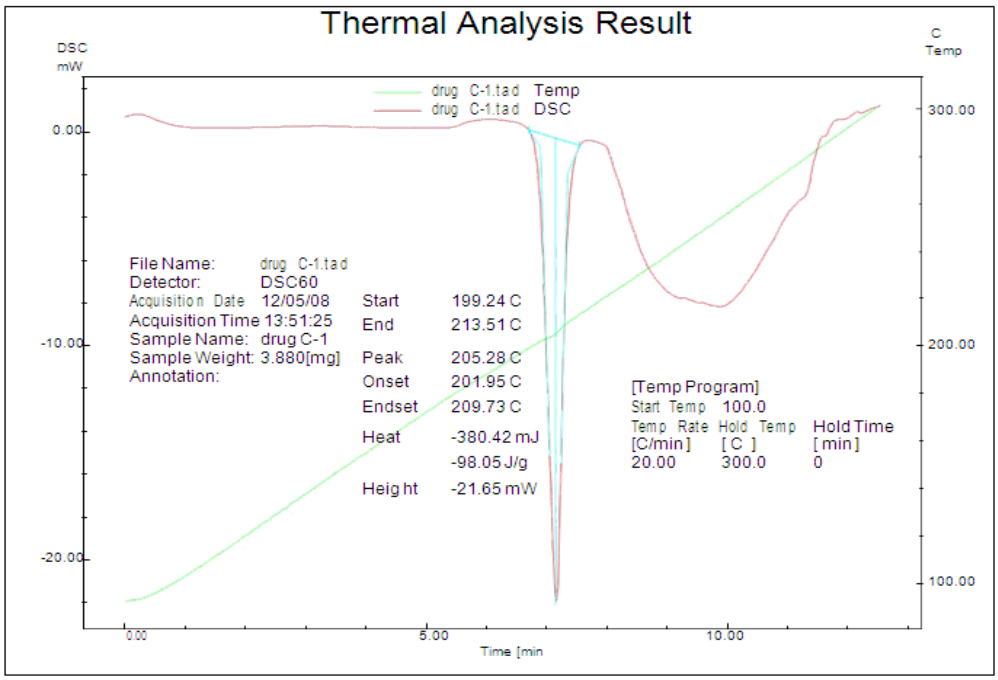

Figure No. 6: DSC thermogram of Piroxicam

f. DSC THERMOGRAM OF PIROXICAM:

The thermogram of piroxicam showed a peak at 7.21 min indicating the melting point of the drug is 199.24^{o}C which is identical to the melting point determined by the open capillary method. The DSC thermogram of piroxicam showed a sharp endothermal peak (200^{o}C).

INFERENCE: The procured sample of piroxicam was characterized by Organoleptic properties, melting point, UV, FTIR and DSC studies. All the observed data were as same as reported in the literature.

Hence, it was the inference that the procured drug sample was of pure piroxicam and hence used for further studies.

B. PREPARATION OF CALIBRATION CURVES:

a. Preparation of calibration curve of piroxicam in distilled water: Absorbance data for calibration curve of piroxicam in distilled water at 358.6 nm:

Table 4: Absorbance data for calibration curve of piroxicam in distilled water at 358.6 nm

Sr. No	Concentration(µg/ml)	Absorbance
1.	0	0
2.	5	0.219
3.	10	0.434
4.	15	0.649
5.	20	0.842
6.	25	1.045
7.	30	1.261

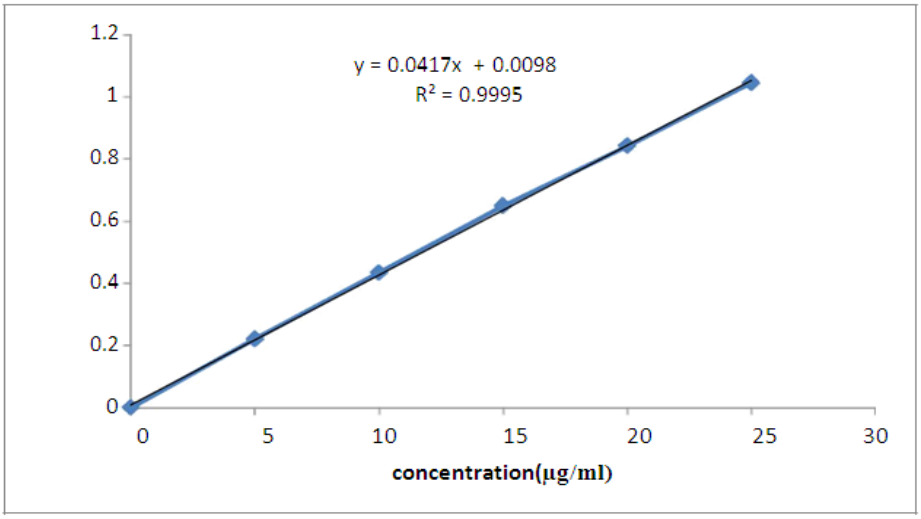

Figure No. 7: Calibration curve of piroxicam in distilled water at 358.6 nm

Prepared calibration curve follows the beers lamberts law, line equation it gives y=0.0417x+0.0098, and regression R^2=0.9995.

b. Preparation of calibration curve of piroxicam in 0.1 N HCL: Prepared calibration curve follows the beers lamberts law, line equation it gives y=0.0777x-0.0063, and regression R^2=0.9993.

Table No. 5: Absorbance data for calibration curve of piroxicam in 0.1 N HCl at 334.4 nm

Sr.No	Concentration(µg/ml)	Absorbance
1.	0	0
2.	2	0.137
3.	4	0.313
4.	6	0.455
5.	8	0.616
6.	10	0.772

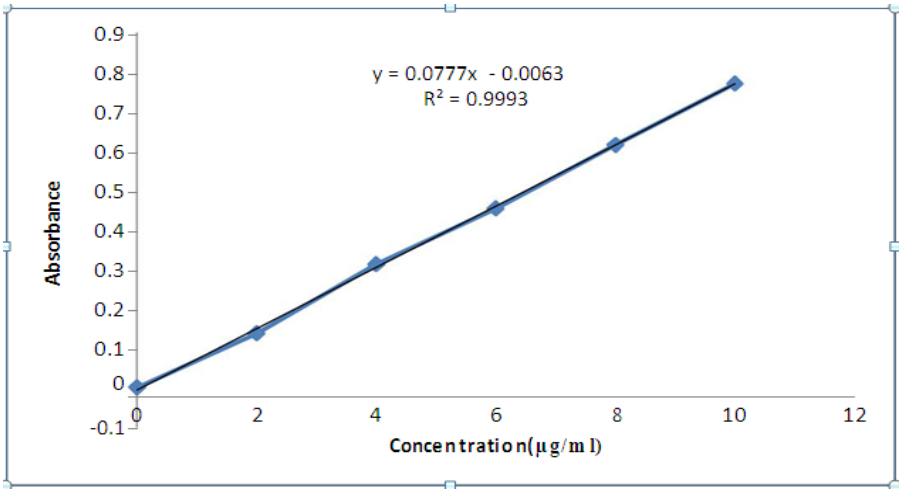

Figure No. 8: Calibration curve of piroxicam in 0.1 N HCl at 334.4 nm

c. Preparation of calibration curve of piroxicam in simulated saliva fluid (pH6.8):

Prepared calibration curve follows the beers lamberts law, line equation it gives y=0.0344x+0.0254, and regression R^2=0.9953.

Table No. 6: Absorbance data for calibration curve of piroxicam in simulated saliva fluid pH 6.8 at 358.4 nm

Sr.No	Concentration(µg/ml)	Absorbance
1.	0	0
2.	5	0.202
3.	10	0.387
4.	15	0.564
5.	20	0.722
6.	25	0.856

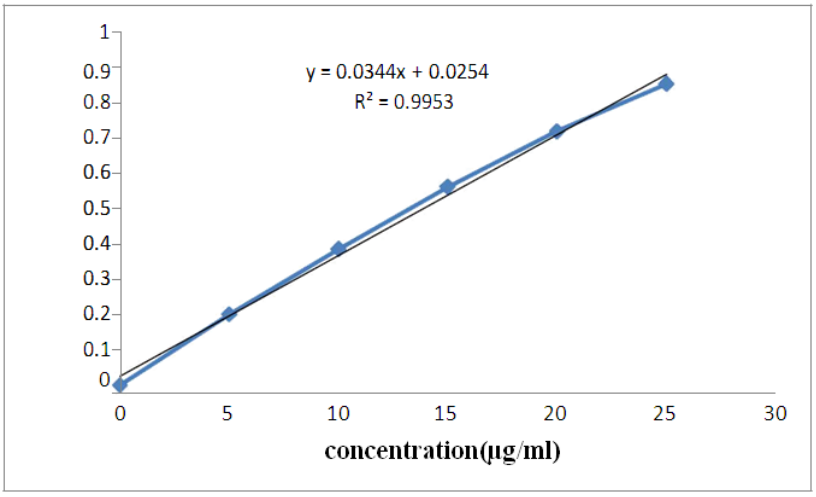

Figure No. 9: Calibration curve of piroxicam in simulated saliva fluid pH 6.8

C. DETERMINATION OF SOLUBILITY OF PIROXICAM:

Table No. 7: The solubility of piroxicam in different mediums

Sr. No	Solvent	Solubility(mg/ml)	Solubility(% w/v)
1.	Distilled Water	0.072	0.007
2.	0.1 N HCL	0.093	0.009
3.	6.8 pH phosphate buffer	0.050	0.005

Solubility study shows that low solubility of piroxicam in phosphate buffer and distilled water.

D. SELECTION OF WATER-SOLUBLE CARRIERS:

Table No. 8: Equilibrium solubility of piroxicam in different water-soluble additives (solubilizers)

Sr. No	Solubilizers	Concentration (%w/v)	Solubility (%w/v)	Solubility enhancement ratio
1.	Distilled water	-	0.007	-
2.	SB	40	1.709	244.14
3.	SC	40	0.115	16.42
4.	NM	40	0.670	95.71
5.	HP-BCD	40	0.561	80.11
6.	PEG 400	40	0.057	8.14
7.	PEG 8000	40	0.059	8.42
8.	PVP K 30	40	0.057	8.14

Where the highest solubility was obtained in 40% sodium benzoate solution. Then, to decrease the concentration of sodium benzoate, different combinations of above mentioned water-soluble additives in different ratios were tried to determine enhancement in solubility keeping the total concentration of solubilizers 40%w/v (constant). So, all possible combinations of two water-soluble additives were taken in such a way that total concentration was always 40% with a fixed ratio of 20:20.

The blends of two water-soluble additives providing the solubility enhancement more than 90 folds have been noted below:

Table No. 9: Blends of soubilizer and Solubility

Sr. No	Blends of solubilizers	Total Conc. (%w/v)	Ratio	Solubility (%w/v)	Solubility enhancement ratio
1.	SB+PVP	40	20:20	0.807	115.28
2.	SB+PEG 8000	40	20:20	0.699	99.85
3.	SB+NM	40	20:20	1.405	200.71
4.	SB+SC	40	20:20	0.650	92.85
5.	SB+HP-BCD	40	20:20	0.989	141.27
6.	NM+HP-BCD	40	20:20	0.870	124.28

Where, SB= sodium benzoate, SC= sodium citrate, NM= niacinamide, HP-BCD= hydroxypropyl beta-cyclodextrin, PEG 400= polyethylene glycol 400, PEG= polyethylene glycol 8000 and PVP K 30=polyvinyl pyrrolidone K 30

Then, all possible combinations of 3 water-soluble additives were taken in such a way that total concentration was always 40% with a fixed ratio of 13.4:13.3:13.3.

The blends of three water-soluble additives providing the solubility enhancement more than 125 folds have been noted below:

Table No. 10: Blends of soubilizer and Solubility

Sr. No	Blends of solubilizers	Total Conc. (%w/v)	Ratio	Solubility (%w/v)	Solubility enhancement ratio
1.	SB+PEG400+PVP	40	13.4+13.3+13.3	1.505	215.10
2.	SB+PEG 8000+PVP	40	13.4+13.3+13.3	1.535	219.28
3.	SB+HP-BCD+PVP	40	13.4+13.3+13.3	1.725	246.42
4.	SB+NM+SC	40	13.4+13.3+13.3	1.110	158.57
5.	NM+HP-BCD+PVP	40	13.4+13.3+13.3	1.274	182.01
6.	NM+PEG8000+PVP	40	13.4+13.3+13.3	0.910	130.00

Where, SB= sodium benzoate, SC= sodium citrate, NM= niacinamide, HP-BCD= hydroxy propyl beta cyclodextrin, PEG 400= polyethylene glycol 400, PEG= polyethylene glycol 8000 and PVP K 30=polyvinyl pyrrolidone K 30.

Then, possible combinations of 4 water-soluble additives were taken in such a way that total concentration was always 40% with the fixed ratio of 10:10:10:10. The blends of four water-soluble additives providing the solubility enhancement more than 125 folds have been noted below:

Table No. 11: Blends of soubilizer and Solubility

Sr. No	Blends of solubilizers	Total Conc. (%w/v)	Ratio	Solubility (%w/v)	Solubility enhancement ratio
1.	SB+PEG400+PVP+NM	40	10:10:10:10	0.923	131.85
2.	SB+PEG8000+PVP+NM	40	10:10:10:10	0.987	141.00
3.	SB+HP-BCD+PVP+NM	40	10:10:10:10	1.163	166.14
4.	SB+NM+SC+HP-BCD	40	10:10:10:10	0.945	135.12

Where, SB= sodium benzoate, SC= sodium citrate, NM= niacinamide, HP-BCD=hydroxyl propyl beta cyclodextrin, PEG 400= polyethylene glycol 400, PEG= polyethylene glycol 8000 and PVP K 30=polyvinyl pyrrolidone K 30.

The blend with maximum solubility enhancement SB+HP-BCD+PVP-K30 (13.4:13.3:13.3) was further explored (keeping the total concentration of solubilizers constant 40 %) by changing the ratio so that maximum solubility can be obtained.

Equilibrium solubility of piroxicam in different Ratio of (SB+HPBCD+PVP K30) water-soluble additives (solubilizers) was found as follows:

Table No. 12: Blends of soubilizer and Solubility

Sr. No	Blends of solubilizers	Total Conc. (%w/v)	Ratio	Solubility (%w/v)	Solubility enhancement ratio
1.	SB+HP- BCD+PVP	40	15:10:15	1.255	179.28
2.	SB+HP- BCD+PVP	40	15:15:10	1.748	249.71
3.	SB+HP- BCD+PVP	40	10:15:15	1.187	169.57
4.	SB+HP- BCD+PVP	40	15:20:05	1.680	240.00
5.	SB+HP- BCD+PVP	40	20:15:05	1.617	231.10

Where, SB= sodium benzoate, HP-BCD=hydroxyl propyl beta cyclodextrin and

PVP K 30=polyvinyl pyrrolidone K 30.

The blend SB+HP-BCD+PVP K 30 in the ratio of 15:15:10 shown the highest solubility enhancement, so that this optimized blends of solubilizers were selected for the preparation of solid dispersions.

E. DRUG EXCIPIENT COMPATIBILITY STUDIES BY FTIR:

1. Plain drug piroxicam:

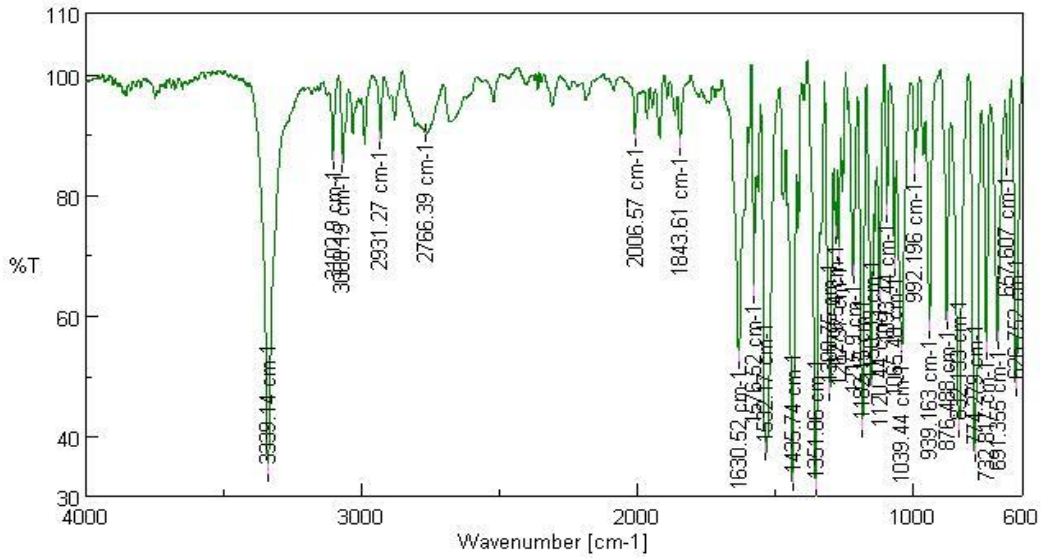

Figure No. 10: IR spectra of piroxicam

2. Excipient: sodium benzoate

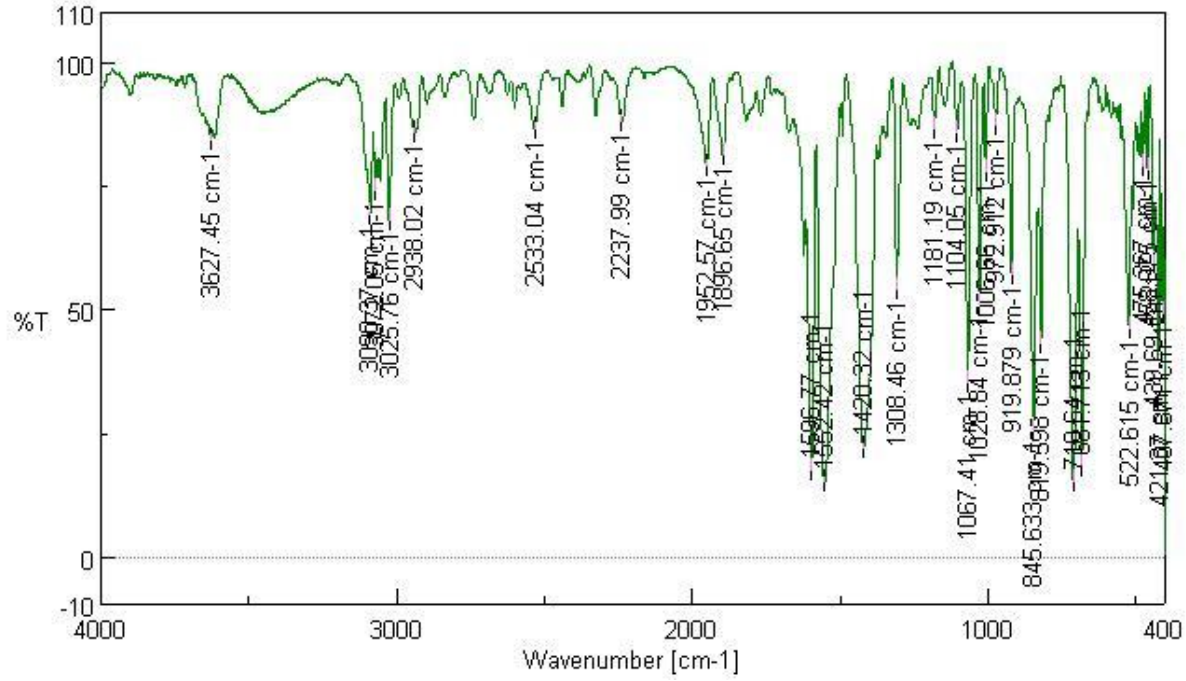

Figure No. 11: IR spectra of sodium benzoate

3. Excipient: PVP k 30

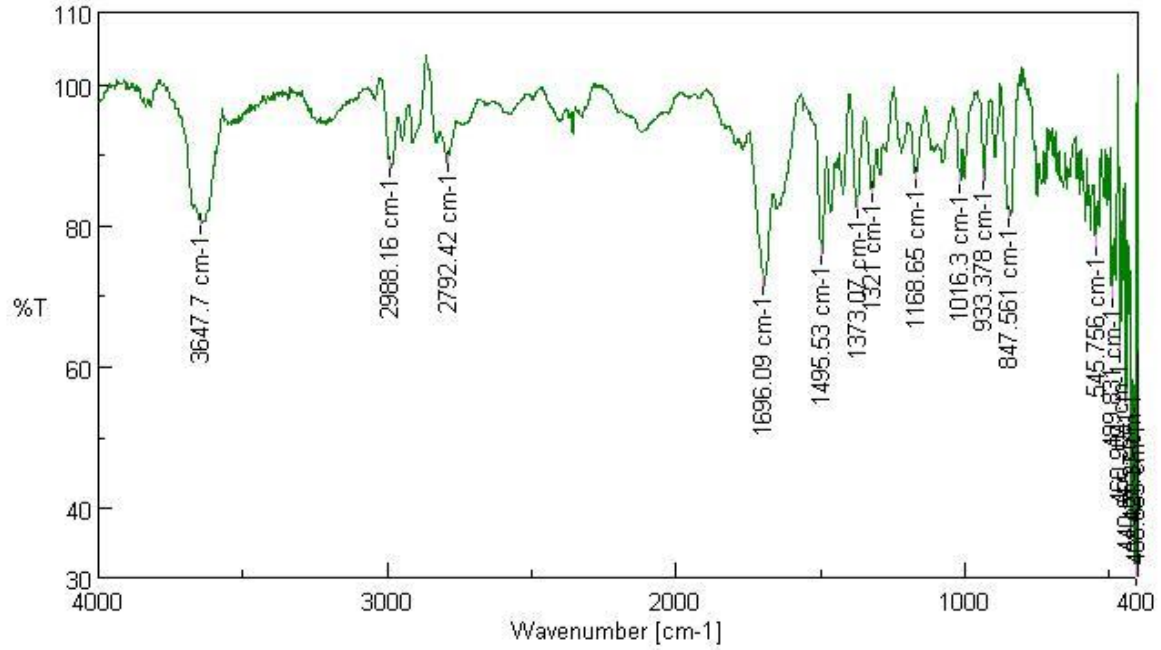

Figure No. 12: IR spectra of PVP K 30

4. Sodium benzoate with piroxicam:

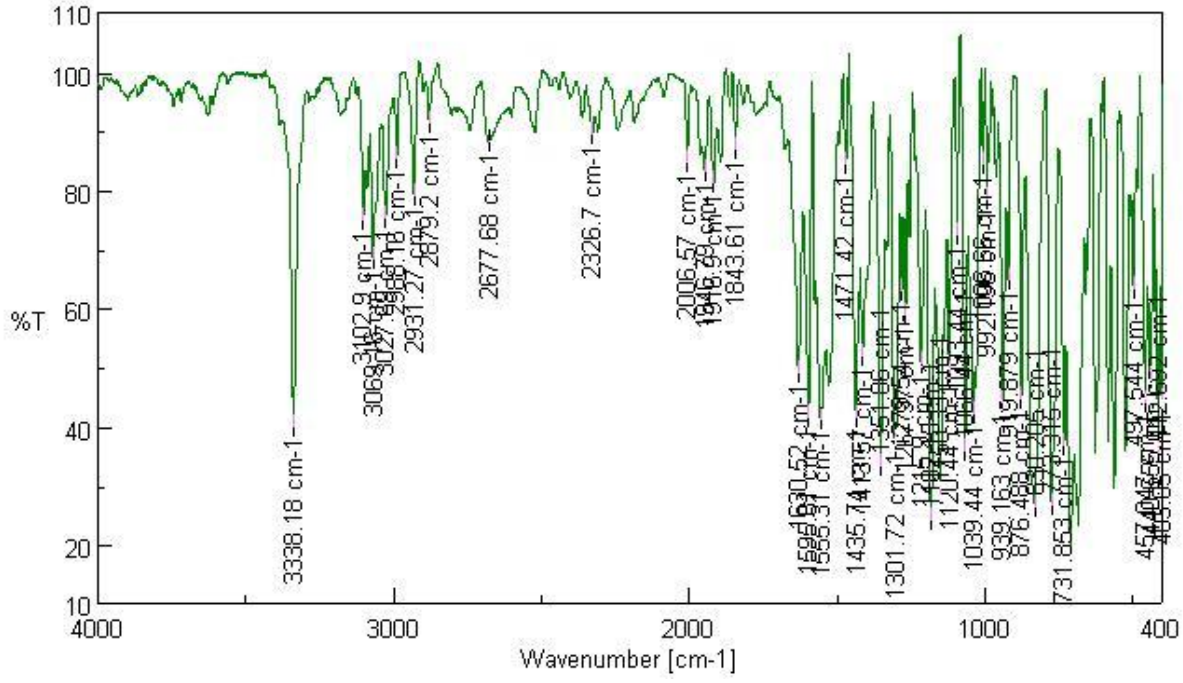

Figure No. 13: IR spectra of sodium benzoate with piroxicam

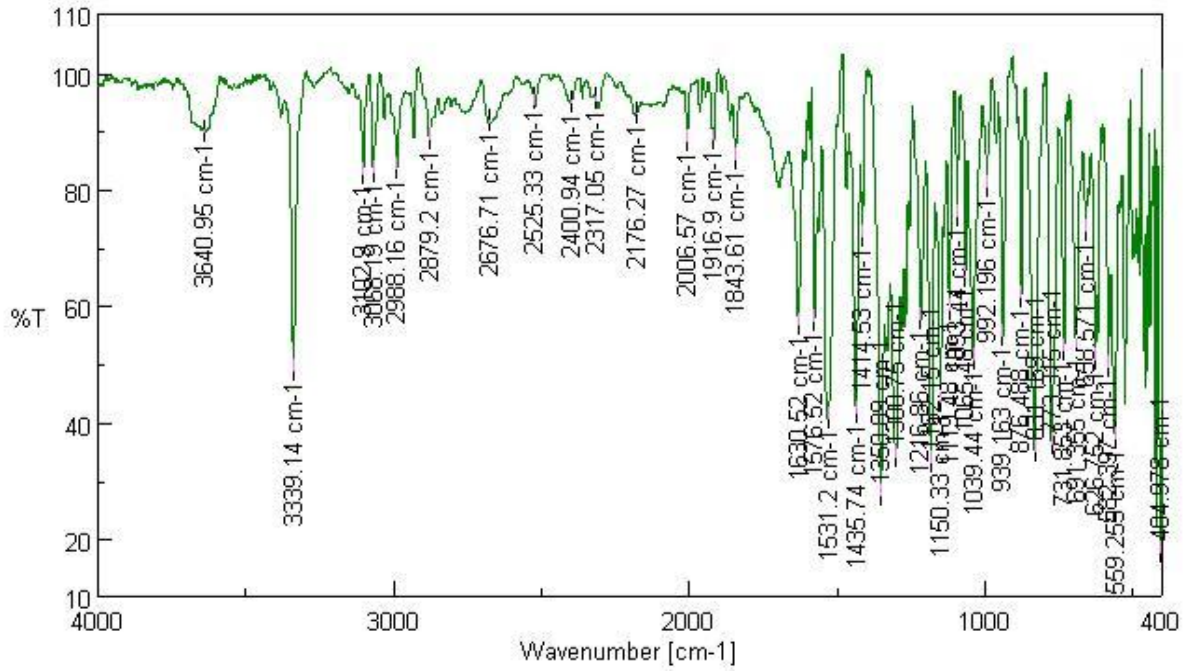

Figure No. 14: IR spectra of PVP K 30 with piroxicam

5. PVP K 30 with piroxicam:

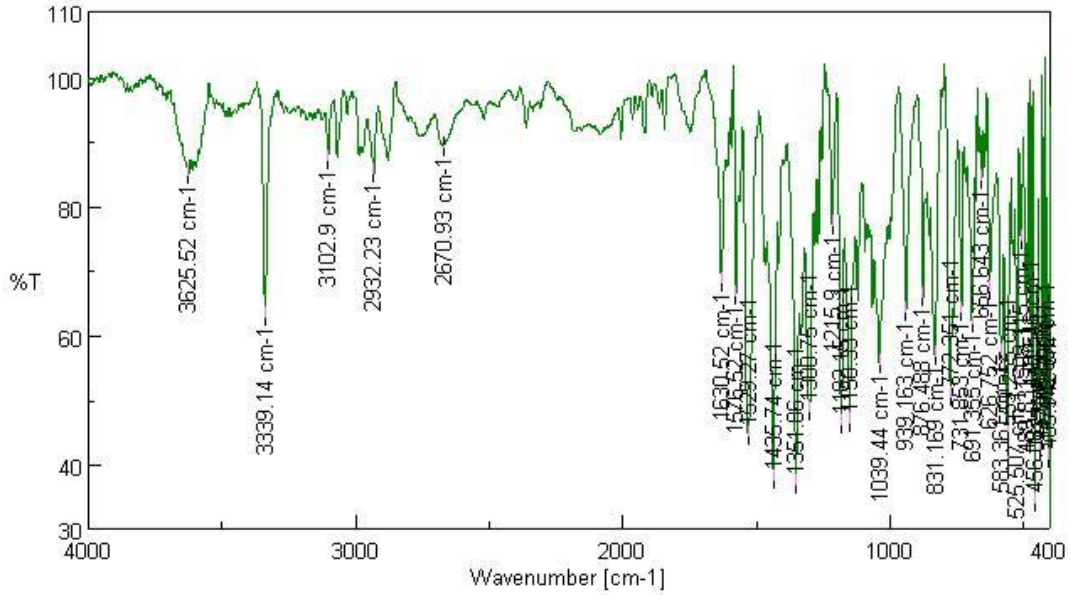

Figure No. 15: IR spectra of HP-BCD with piroxicam

6. HP-BCD with piroxicam:

The FTIR spectral analysis showed that there is the change in percent transmittance which may be due to change in crystallinity and there is no disappearance of any characteristics

peaks of pure drug Piroxicam and in the physical mixture of a drug to polymer, which confirms the absence of chemical interaction between drug and polymers.

F. FORMULATION AND PREPARATION OF SOLID DISPERSIONS OF PIROXICAM BY APPLICATION OF MIXED-SOLVENCY CONCEPT

Table No. 13: Composition of solid dispersion

Sr. No.	Drug: Solubilizres ratio	Piroxicam (gm)	Quantity is taken in gm		
			Sodium benzoate(gm)	HP-BCD(gm)	PVP K 30 (gm)
1.	1:4	1.00	1.50	1.50	1.00
2.	1:6	1.00	2.25	2.25	1.50
3.	1:8	1.00	3.00	3.00	2.00
4.	1:10	1.00	3.75	3.75	2.50
5.	1:12	1.00	4.50	4.50	3.00

G. CHARACTERIZATION OF SOLID DISPERSIONS:

a. Determination of drug content in solid dispersion and physical mixtures:

Table No. 14: Drug content of piroxicam in solid dispersions and physical mixture

Sr. No	Drug: solubilizers ratio	The drug content in % w/w	
		Solid dispersion	Physical mixture
1.	1:4	98.80	99.00
2.	1:6	99.50	100.2
3.	1:8	101.9	99.50
4.	1:10	100.4	101.40
5.	1:12	99.20	100.10

Solid dispersion and in physical mixtures showed acceptable ranges of drug content.

b. Percentage Yield:

Table No. 15: Percentage yield of piroxicam in solid dispersions

Sr. No	Solid Dispersion	Percentage Yield
1	SD 1:4	86.40 %
2	SD 1:6	88.71 %
3	SD 1:8	94.33 %
4	SD 1:10	91.92 %
5	SD 1:12	94.41 %

The percentage yield of piroxicam solid dispersions ratio 1:8, 1:10, 1:12 showed acceptable range.

c. Micromeretic properties of solid dispersion:

Table No. 16: Micromeretic properties of solid dispersion

Sr.No	Parameter	Observation	Inference
1	Angle of repose	34^0 01’	Good flow
2	Tap density	0.868gm/ml	-
3	Bulk density	0.735gm/ml	-
4	Carr’s index	15.32	Fair flow
5	Hausner’s ratio	0.933	Good flow

Micromeretic properties of solid dispersion of piroxicam showed a good flow of powder blend.

d. Solubility Study:

Table No. 17: Solubility Study of solid dispersion is represented

Sr. No	Solid dispersion	Solubility (mg/ml)
1	SD 1:4	0.386
2	SD1:6	0.512
3	SD 1:8	0.670
4	SD 1:10	0.718
5	SD 1:12	0.732

e. *In-vitro* dissolution rate studies:

Comparative accounts of dissolution profiles of a physical mixture containing different drug: solubilizers ratio:

Table No. 18: *In-vitro* dissolution rate studies

Sr. No	Time (min)	% Drug release of physical mixture				
		1:4	1:6	1:8	1:10	1:12
1.	1	20.04	22.33	35.45	39.13	42.17
2.	5	35.58	41.67	58.34	67.70	66.58
3.	10	41.15	55.94	69.77	78.54	79.45
4.	15	44.52	58.49	75.66	81.25	83.34
5.	20	47.35	62.84	81.25	85.34	87.17
6.	30	50.11	73.22	84.51	88.32	89.25

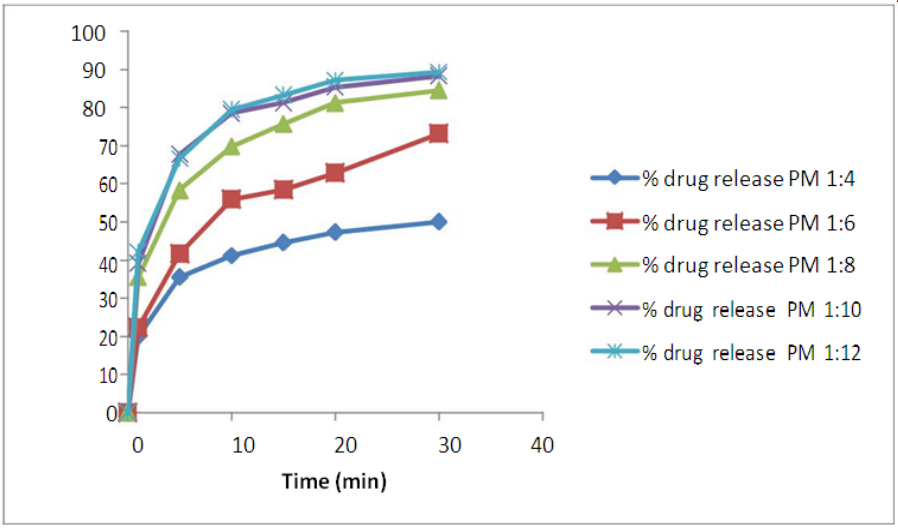

Figure No. 16: A comparative account of dissolution profiles of physical mixture

Table No. 19: A comparative account of dissolution profiles of solid dispersions containing different drug: solubilizers ratio

Sr. No	Time (min)	% Drug release of solid dispersion				
		1:4	1:6	1:8	1:10	1:12
1.	1	34.13	44.55	85.09	82.77	67.72
2.	5	36.44	49.76	96.10	91.46	74.09
3.	10	43.97	56.71	100.73	98.99	80.46
4.	15	48.61	61.35	100.15	100.15	89.15
5.	20	57.29	67.72	99.57	100.15	98.41
6.	25	60.77	75.83	98.41	98.41	97.25
7.	30	67.72	79.30	98.99	98.99	98.99
8.	45	78.14	86.83	-	-	-
9.	60	91.46	94.94	-	-	-

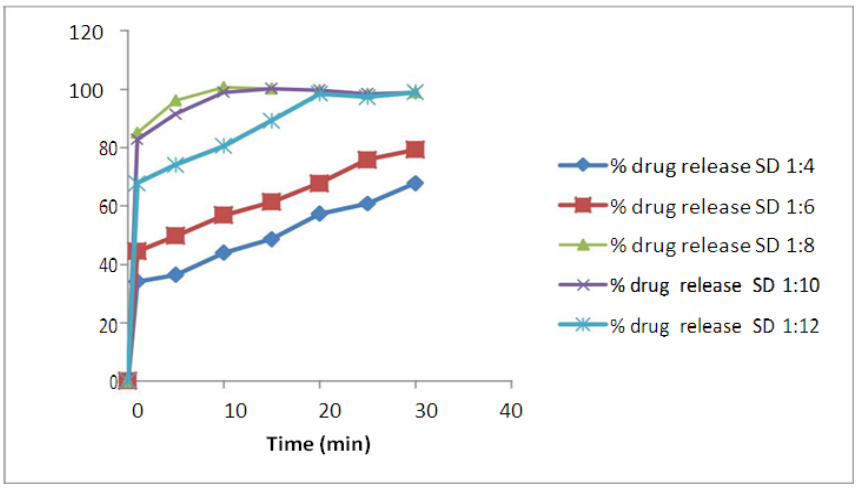

Figure No. 17: Comparative account of dissolution profiles of solid dispersions

Table No. 20: A comparative account of dissolution profiles of piroxicam pure drug, physical mixture, solid dispersion

Sr. No	Time(min)	% Drug release		
		Pure drug	PM 1:8	SD 1:8
1.	1	2.66	35.45	85.09
2.	5	5.38	58.34	96.10
3.	10	8.27	69.77	100.73
4.	15	10.18	75.66	100.15
5.	20	11.92	81.25	99.57
6.	25	13.37	82.48	98.41
7.	30	14.99	84.51	98.99

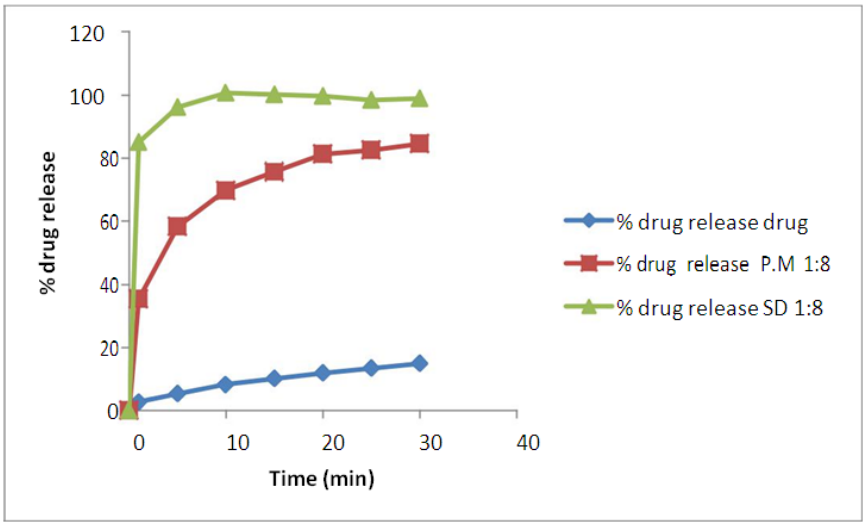

Figure No. 18: A comparative account of dissolution profiles of pure drug, physical mixture 1:8, solid dispersions 1:8

From the above studies, it is evident that solid dispersions of ratio 1:8 to 1:10 were dissolved nearly completely within 1 minute, and when observed visually, they were found to be dissolved only within 40-50 seconds. While, on the other hand, the solid dispersions of ratio 1:4, 1:6 and physical mixture dissolved completely even after 30 minutes.

Since there was a significant improvement in dissolution rate when drug: solubilizers were used in 1:8 and 1:10 ratio. The dissolution profiles from these two solid dispersions were almost the same. To minimize the quantity of solubilizing agents, a 1:8 ratio was considered to be the optimum ratio.

This optimized solid dispersion filled in a hard gelatin capsule and perform a dissolution study and compared it with marketed capsule formulation.

Table No. 21: A comparative account of dissolution profiles of piroxicam marketed capsule and prepared capsule formulation

Sr. No	Time(min)	Marketed capsule	% drug release Prepared Capsule formulation
1.	5	15.17	83.51
2.	10	28.12	95.24
3.	15	43.51	99.57
4.	20	59.64	100.15
5.	25	71.35	100.74
6.	30	82.76	99.57
7.	35	86.58	-

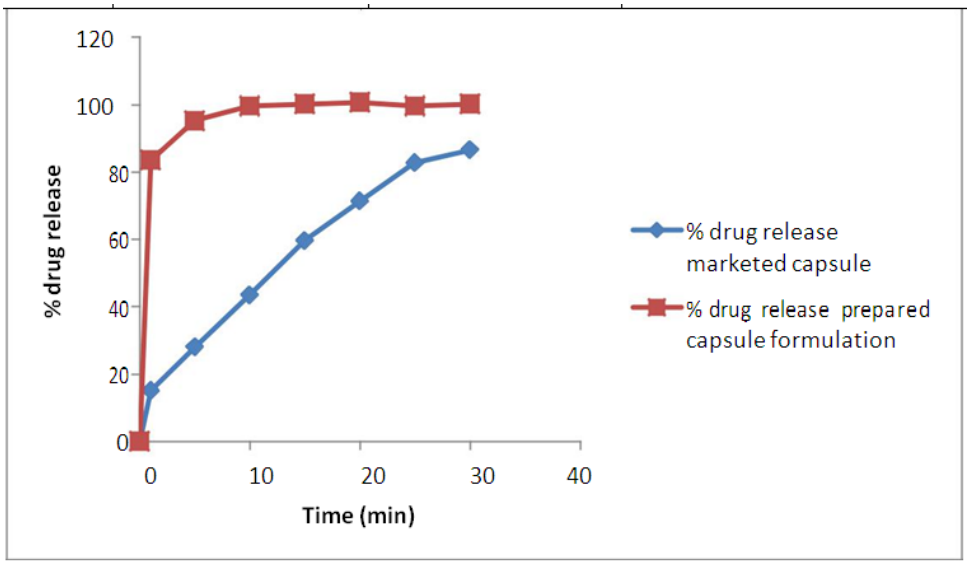

Figure No. 19: Comparative account of dissolution profiles of piroxicam marketed capsule and prepared capsule formulation

These capsule formulation withdrawal of sample in 5, 10, 15, 20, 25, 30 and 35 min. in that shows prepared capsule formulation was better to release than that of marketed capsule formulation.

f. Fourier transforms IR spectroscopy:

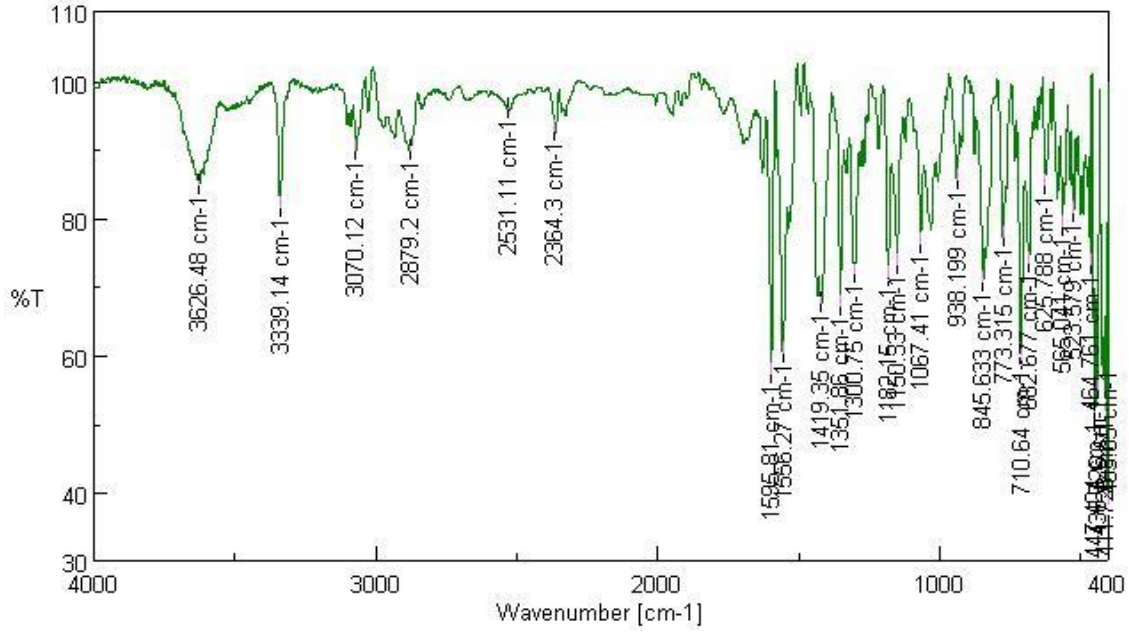

Figure No. 20: IR spectra of a physical mixture of 1:8

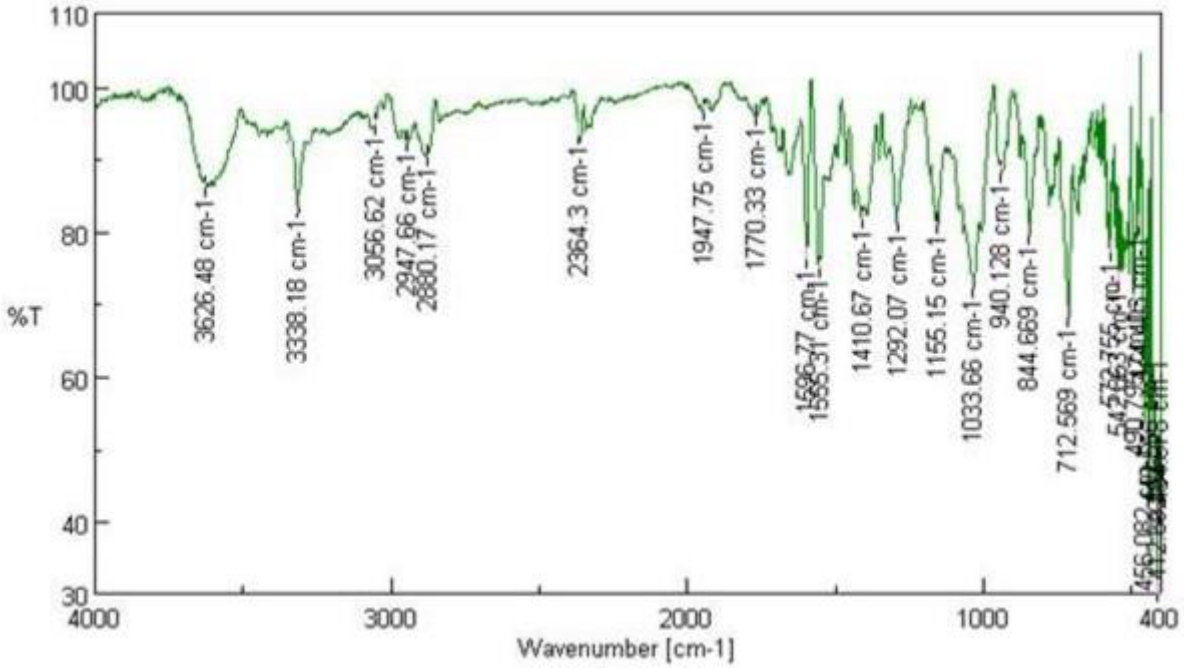

Figure No. 21: IR spectra of Solid dispersion 1:8Peaks given by piroxicam spectra are present in the FTIR spectra of solid dispersions and physical mixture.

The only change of percent transmittance due to changes of crystalline to amorphous form.

g. Differential Scanning Calorimetry (DSC):

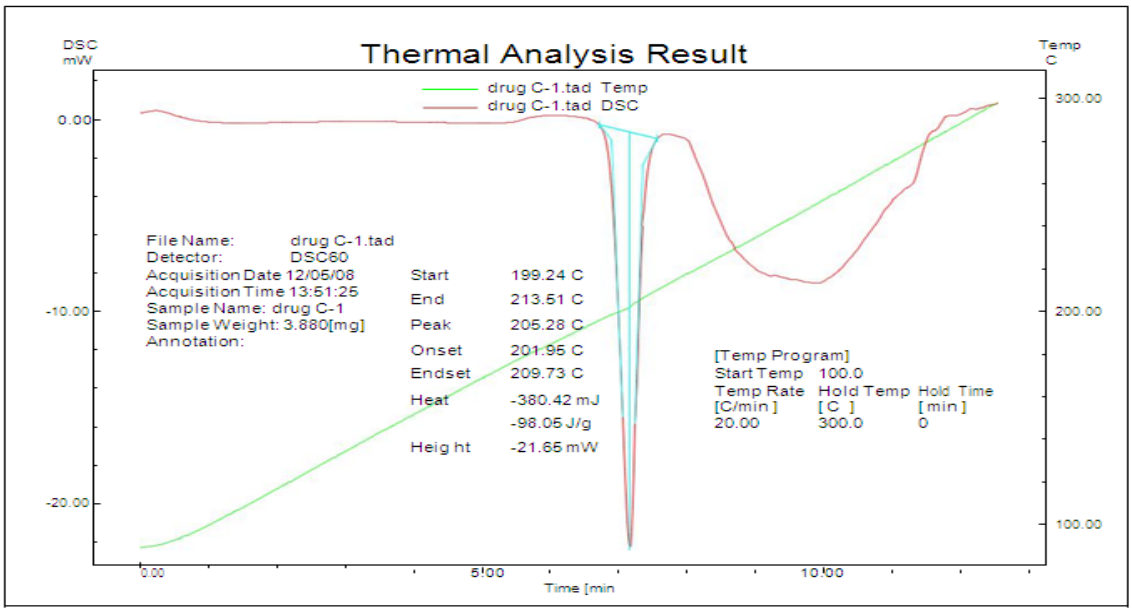

Figure No. 22: DSC thermogram of piroxicam

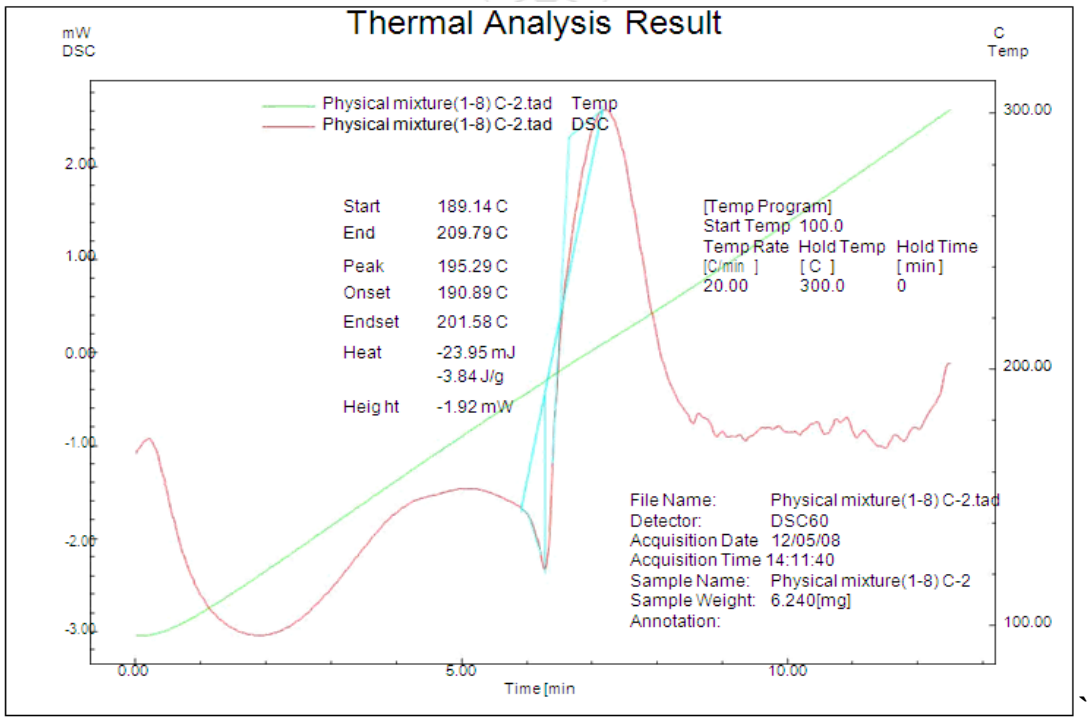

Figure No. 23: DSC thermogram of physical mixture 1:8

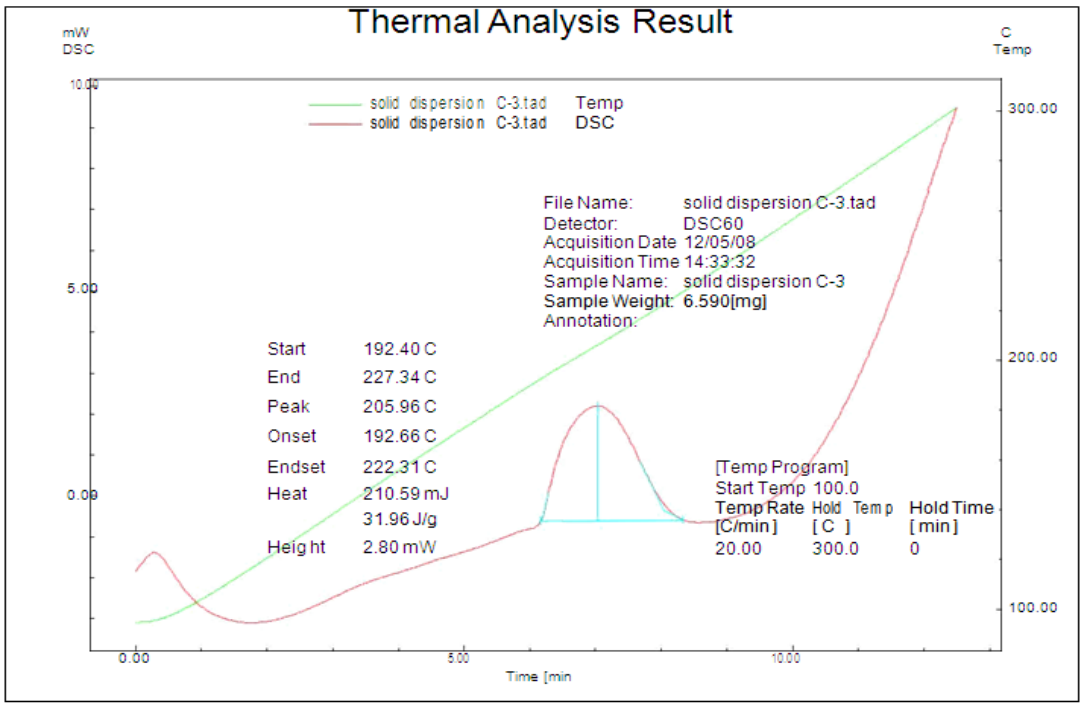

Figure No. 24: DSC thermogram of solid dispersion 1:8

The DSC curve of pure piroxicam exhibited a single endothermic response corresponding to the melting of the drug. The onset of melting was observed at 201.95°C, whereas pure PVP K 30 showed a melting endotherm at 100.41°C. Thermograms of SDs showed the absence of a piroxicam peak, suggesting that piroxicam is completely soluble in the liquid phase of polymer or absence of crystalline nature of piroxicam. However, the melting peak of PVP K 30 in SDs was observed at a slightly lower temperature (97-100°C) than that of pure PVP K 30. The PMs formulation of piroxicam and PVP K 30 also showed no endothermic peak of piroxicam. It is speculated that piroxicam dissolved in PVP K 30 during the DSC measurement, only one endothermic peak at 103.33°C corresponding to PVP K 30 was observed.

h. Powder x-ray diffraction studies (XRD): Random orientation of a crystal lattice in a powder sample causes the X-ray to scatter in a reproducible pattern of peak intensities at distinct angles (θ) relative to the incident beam. Each diffraction pattern is characteristic of a specific crystalline lattice for a given compound. an amorphous form does not produce a pattern. X-ray diffractogram of piroxicam, physical mixture and an optimized batch of solid dispersions are given in figures below:

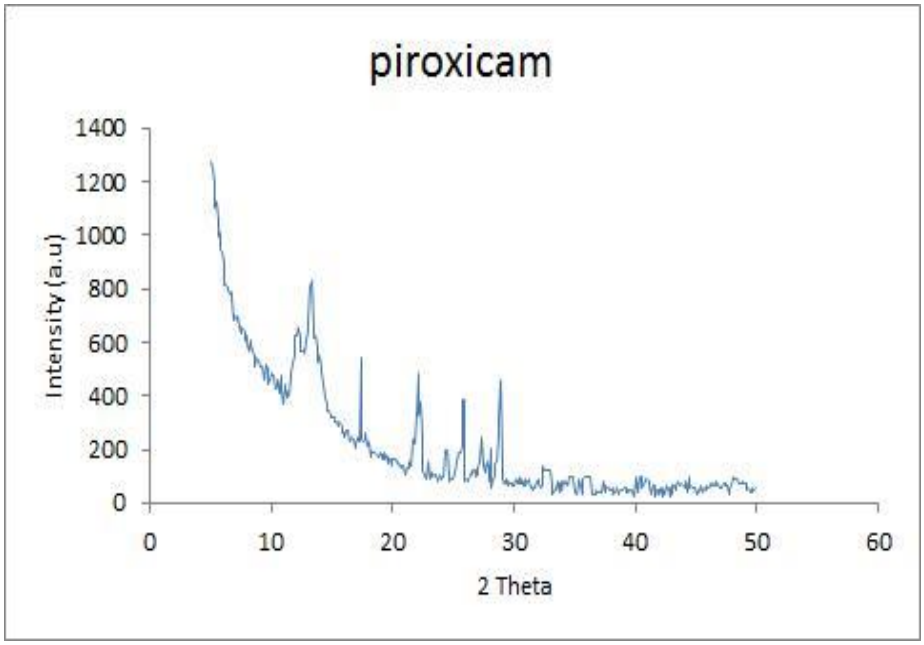

Figure No. 25: X-ray diffractogram of piroxicam drug sample

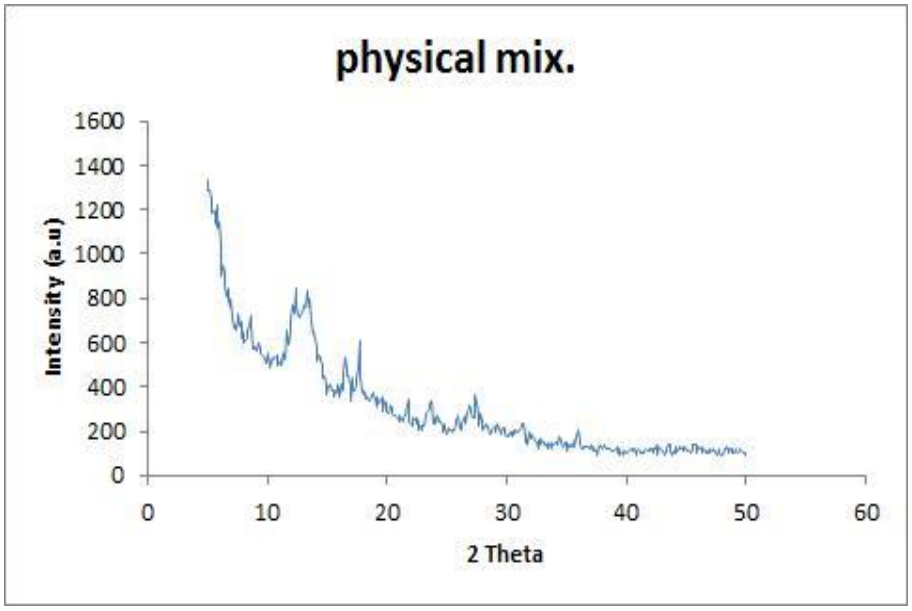

Figure No. 26: X-ray diffractogram of physical mixture 1:8

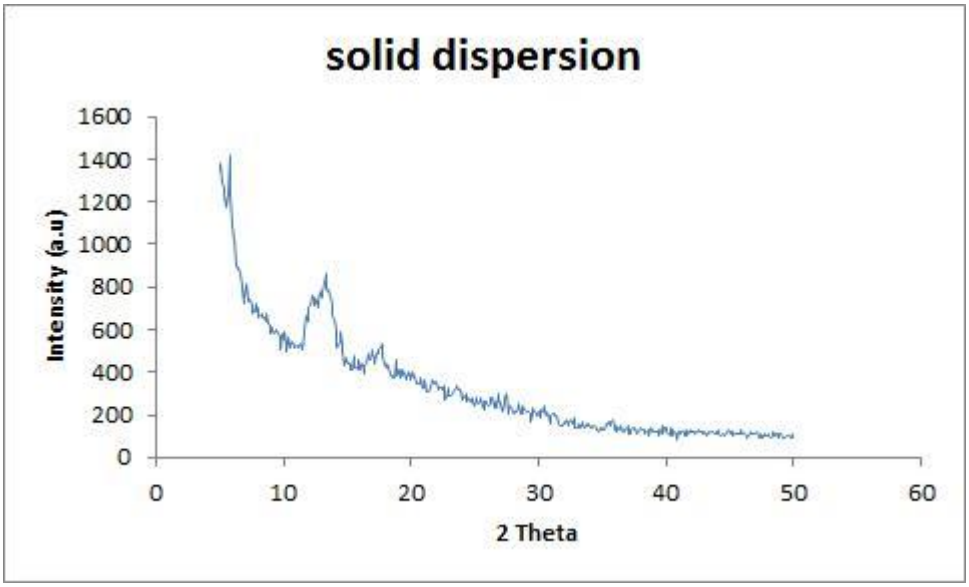

Figure No. 27: X-ray diffractogram of solid dispersion 1:8

The X-ray diffractogram of piroxicam has sharp peaks at diffraction angles (2θ) 13.10°, 13.40°, 18.50°, 22.10°, and 28.90° showing a typical crystalline pattern. However, all major characteristic crystalline peaks appear in the diffractogram of solid dispersions and physical mixture system but of low intensity. This indicates that some amount of drug converts to its amorphous form. IR and DSC studies support the same hypothesis, which is confirmed by x-ray diffractometry**.**

SUMMARY AND CONCLUSION

The present research study aimed to explore the possibility of employing mixed solvency techniques in the formulation of a poorly water-soluble drug. In the present study, practically water-insoluble drug, piroxicam was tried to be solubilized by employing the combination of physiologically compatible water-soluble additives (solubilizers) to attempt its Immediate-release formulations.

For identification and characterization of drug spectrophotometric analysis, FTIR spectroscopy, X-ray diffraction study, differential scanning calorimetry study and melting point determination of the drug sample were carried out. The drug complied with the tests prescribed in the reported kinds of literature.

The calibration curve of the drug was prepared in the distilled water, 0.1 N HCl and simulated saliva fluid (pH 6.8). The linearity of calibration curve showed that the Beer

Lambert's law was obeyed in the concentration range of 5-30 µg/ml at the λmax of 358.6 nm in Distilled water and in the concentration range 2-10 µg/ml at the λmax of 333.4 nm in 0.1 N HCl, and in the concentration range 5-25 µg/ml at the λmax of 358.4 nm in simulated saliva fluid (pH 6.8).

Preformulation study of the drug was carried out to determine the solubility of a drug in water. Aqueous solubility of the drug was found to be 0.007 % w/v. Drug excipients physical compatibility study was done observing no any physical changes in the blends of drug and excipient visually for one month. it also Drug excipients FTIR compatibility study was performed in that observed no interaction between drug and excipients.

UV interference study for drug estimation was also done taking drug concentration 10 µg/ml and excipient concentration 1000 µg/ml against distilled water as the reagent blank. These studies showed no physical incompatibility and no UV interference.

For selection of water-soluble additives (solubilizers) for preparation of solid dispersion, solubility studies were conducted taking water-soluble additives (solubilizers) from the category of hydrotropic agents (sodium benzoate, sodium citrate, and niacinamide) and water-soluble solids (HP-BCD, PEG 8000 and PVP K30) keeping concentration 40 % w/v (constant). The solubility determinations of the drug in these solutions were carried out at room temperature. The solubility was increased up to 244.14 fold in 40 % w/v sodium benzoate solution that was maximum among the individual solubilizers.

To minimize the probable toxic effects of individual solubilizer at high concentrations, the blends of the water-soluble additives (solubilizers) were tried to give the expected solubility. The blends of solubilizers of total strength 40% w/v were used for the solubility studies to get sufficiently high expected solubilities. The combinations of two, three and four agents were tried. The maximum synergistic effect was observed in the blend containing sodium benzoate, HP-BCD and PVP K 30 in 15:15:10 ratio that was 249.71 folds.

From the results of the solubility, determination studies blend of solubilizers SB+HPBCD+PVP K30 (15:15:10) was employed for developing solid dispersion of piroxicam. Different solid dispersions were prepared with a different drug: solubilizer ratio. The ratio of drug: solubilizers were optimized by dissolution studies. Prepared and optimized solid dispersion was compared for dissolution studies with piroxicam pure drug, physical mixture.

Solid dispersion containing drug: solubilizer in ratio 1:8 showed a faster dissolution rate than piroxicam pure drug, physical mixture. After that optimized solid dispersion filled in a hard gelatin capsule and perform dissolution study and compared with marketed capsule formulation. In that shows prepared capsule formulation was better to release than marketed capsule formulation. Piroxicam pure drug prepared solid dispersion and prepared physical mixture were also studied for FTIR, X-ray diffraction study and differential scanning calorimetry that showed no interaction between drug and solubilizers.

From all the above studies, it was concluded that the approach of mixed solvency is novel, safe, cost-effective and user-friendly. It also eliminates the problem of toxicity associated with a high concentration of water-soluble solubilizers. So, it may be employed in dosage form development of drugs where the fast onset of action desired. It may also enhance the bioavailability associated with the poor dissolution of the drug.

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