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NOVEL PHARMACEUTICAL APPLICATION OF MIXED SOLVENCY CONCEPT FOR DEVELOPMENT OF SOLID DISPERSIONS OF PIROXICAM

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ABSTRACT

Based on the large number of experiments on solubilization of poorly water-soluble drugs ,The auther is of the opinion that hydrotropy is another type of cosolvency and all water soluble substances whether solids, liquids or gases have solubilizing properties. Therefore, an aqueous solution containing small quantities of several water-soluble excipients giving a concentrated solution may act as a solvent system for some poorly water-soluble drugs. This is example of the concept of mixed solvency. This same concept has been explored to formulate the solid dispersions of poorly water soluble drug piroxicam. And Solid dispersions were evaluated for flow property, powder x-ray diffraction, differential scanning calorimetric studies, scanning electron microscopy, dissolution studies and stability studies.

KEYWORDS: Mixed solvency, hydrotropy, piroxicam, solid dispersion.

INTRODUCTION

Maheshwari [1-5] has proposed the mixed-solvency concept. The mixed solvency concept states that all substances whether liquids, gases or solids possess solubilizing power. In order to improve aqueous solubility of a poorly water-soluble drug, the concentrated aqueous solution containing various dissolved excipients (liquids and solids both) can give successful results. In one of the study it was found that additive and synergistic solvent action on the solubility of salicylic acid could be obtained by using aqueous solutions containing different excipients (liquids and solids both). Mixed-solvency concept shall be helpful to formulate

various dosage forms of insoluble drugs utilizing safe concentrations of excipients for solubilization. The solubility of a large number of drugs have been enhanced by the application of mixed solvency concept. [1-20]

In the present investigation, mixed solvency concept has nicely be used to prepare solid dispersion of a poorly water soluble drug, piroxicam, employing solubilizing power of solid excipients. The solid dispersions were evaluated for flow property, powder X-ray diffraction, differential scanning calorimetric studies, scanning electron microscopy, dissolution studies and chemical stability studies.

EXPERIMENTAL

MATERIAL AND METHODS

A Shimadzu UV/Visible spectrophotometer (Model-UV 1700) with 1 cm matched silica cells was employed. Piroxicam was obtained from Shreya Life Science Pvt. Ltd., Aurangabad (India).

1. PREPARATION OF CALIBRATION CURVE OF PIROXICAM IN DM WATER

Fifty mg of piroxicam was accurately weighed and transferred to a 100 ml volumetric flask. To this, 80 ml of methanol was added to dissolve the drug and the volume was made up to 100 ml with methanol. Then, 10 ml of this solution was taken in another 100 ml volumetric flask and volume was made up to 100 ml with DM water. The concentration of this resulting solution (stock solution) was 50 µg/ml. Appropriate dilutions were made from stock solution with DM water in concentration range of 5-30 µg/ml. The absorbances of the resulting drug solutions were observed using a double beam UV/Visible spectrophotometer (Shimadzu A-160) at 358 nm against the respective reagent blanks. The data is recorded in table1.

Table 1: Absorbance data for calibration curve of piroxicam in DM water at 358 nm

S.NO.	Concentration (6g/ml)	Absorbance
1.	0	0.000
2.	5	0.219
3.	10	0.434
4.	15	0.649
5.	20	0.842
6.	25	1.045
7.	30	1.261

PREPARATION OF CALIBRATION CURVE OF PIROXICAM IN 0.1N HCl

Fifty mg of piroxicam was accurately weighed and transferred to a 100 ml volumetric flask. To this, 80 ml of methanol was added to dissolve the drug and the volume was made upto 100 ml with methanol. Then, 10 ml of this solution was taken in another 100 ml volumetric flask and volume was made upto 100 ml with 0.1N HCl. The concentration of this resulting solution (stock solution) was 50 µg/ml .Appropriate dilutions were made from stock solution with 0.1N HCl in concentration range of 2-10 µg/ml. The absorbances of the resulting drug solutions were observed at 333nm using a double beam UV/Visible spectrophotometer.

Table.2: Absorbance data for calibration curve of piroxicam in 0.1 HCl at 333 nm

S.N.	Concentration (6g/ml)	Absorbance
1	0	0
2	2	0.137
3	4	0.313
4	6	0.455
5	8	0.616
6	10	0772

SOLUBILITY STUDIES

Solubility studies in different aqueous mediums were carried out by adding an excess amount of drug (piroxicam) in the 5 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 and solutions were allowed to equilibrate for 24 hrs. Then, the solutions were transferred into centrifuge tubes and centrifuged at about 2000 rpm for 5 min. and solutions were filtered through Whatman grade 41 filter. One ml of the filtrate was suitably diluted with the respective medium. The absorbances of the solutions were measured at 358 nm (333 nm in case of 0.1 N HCl) on a double beam UV/Visible spectrophotometer .The results are reported in table 3.

SOLUBILITY OF PIROXICAM IN DIFFERENT MEDIUM

Table 3: Solubility of piroxicam in different medium

S.NO.	Solvent	Solubility (mg/ml)	Solubility (% w/v)	Description
1	DM water	0.067	0.007	Practically insoluble
2	0.1 N HCl	0.056	0.006	Practically insoluble
3	6.8 pH phosphate	0.050	0.005	Practically insoluble
	Buffer			

4. PH DEPENDENT SOLUBILITY OF PIROXICAM

For determination of pH dependent solubility, buffer solutions were prepared from pH 1.2 to ph 10.Solubility studies were done in the same way (mentioned earlier).The results are presented in table 4.

Table 4: pH dependent solubility of piroxicam.

S.NO	Buffer (pH)	Solubility (mg/ml)	Solubility (% w/v)	Description
1	Hydrochloric acid buffer Ph 1.2	0.056	0.005	Practically insoluble
2	Hydrochloric acid buffer pH 2.0	0.050	0.005	Practically insoluble
3	Acid phthalate buffer pH 3.0	0.055	0.005	Practically insoluble
4	Acid phthalate buffer pH 4.0	0.055	0.005	Practically insoluble
5	Neutralized phthalate buffer pH 5.0	0.048	0.005	Practically insoluble
6	Phosphate buffer pH 6.0	0.056	0.005	Practically insoluble
7	Phosphate buffer pH 7.0	0.317	0.032	Very slightly Soluble
8	Phosphate buffer pH 8.0	0.578	0.058	Very slightly Soluble
9	Alkaline borate buffer pH 9.0	1.656	0.166	Slightly soluble
10	Alkaline borate buffer pH 10.0	2.783	0.278	Slightly soluble

5. SELECTION OF WATER-SOLUBLE CARREIRS

All water soluble substances whether liquids, solids or gases may act as solubilizer for poorly water soluble drugs. Therefore for the present investigation several solubilizing additives from the category of hydrotropic agents (sodium benzoate, sodium acetate, sodium citrate, urea and niacinamide) and water soluble solids (PEG 4000, PEG 6000 and PVP K 30) were selected. For 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 total 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 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 centrifuge and then solutions were filtered through Whatman grade 41 filter. Aliquot was suitably diluted with DM water and analyzed using UV spectrophotometer at 358 nm against corresponding reagent blanks. Show in table 5,6,7,8,9.

Table 5: Equilibrium solubility of piroxicam in different water-soluble additives (solubilizers)

S.N.	Solubilizers	Concentration (% w/v)	Solubility (% w/v)	Solubility Enhancement Ratio
1.	DM water	-	0.006	-
2.	SB	40	1.709	253.327
3.	SA	40	0.115	17.057
4.	SC	40	0.029	4.339
5.	UR	40	0.317	47.042
6.	NM	40	0.670	99.283
7.	P4K	40	0.057	8.531
8.	P6K	40	0.057	8.459
9.	PVP	40	0.057	8.459

Table 6: Equilibrium solubility of piroxicam in different blends containing four water-soluble additives (solubilizers)

S. .NO	Blends of Solubilizers	Total conc. (% w/v)	Ratio	Solubility (% w/v)	Solubility Enhancement Ratio
1.	SB+PVP+P4K+NM	40.00	10:10:10:10	0.923	136.898
2.	SB+PVP+P6K+NM	40.00	10:10:10:10	0.986	146.213
3.	SB+SA+UR+NM	40.00	10:10:10:10	1.163	172.364
4.	SB+SA+UR+SC	40.00	10:10:10:10	0.416	61.668
5.	SB+SA+SC+NM	40.00	10:10:10:10	0.851	126.151
6.	SB+SC+UR+NM	40.00	10:10:10:10	0.945	140.123
7.	SC+SA+UR+NM	40.00	10:10:10:10	0.711	105.373
8.	SC+SA+UR+NM	40.00	10:10:10:10	0.711	105.373

Where, SB= sodium benzoate, SA= sodium acetate, SC= sodium citrate, UR= urea,NM= niacinamide, P4K= PEG 4000, P6K= PEG 6000 and PVP= PVP K 30

Table 7: Equilibrium solubility of piroxicam in different blends containing three water-soluble additives (solubilizers)

S.NO.	Blends of Solubilizers	Total conc. (% w/v)	Ratio	Solubility (% w/v)	Solubility Enhancement Ratio
1.	PVP+P4K+SB	40.00	13.3:13.3:13.3	1.724	255.476
2.	PVP+P6K+SB	40.00	13.3:13.3:13.3	1.535	227.534
3.	SB+SA+UR	40.00	13.3:13.3:13.3	0.701	103.940
4.	SB+SA+NM	40.00	13.3:13.3:13.3	1.269	188.127
5.	SB+NM+UR	40.00	13.3:13.3:13.3	1.204	178.454

6.	NM+SA+UR	40.00	13.3:13.3:13.3	0.880	130.450
7.	SB+SA+SC	40.00	13.3:13.3:13.3	0.370	54.861
8.	SB+SC+UR	40.00	13.3:13.3:13.3	0.544	80.654
9.	SB+SC+NM	40.00	13.3:13.3:13.3	1.110	164.483
11.	SC+SA+NM	40.00	13.3:13.3:13.3	0.665	98.566
12.	NM+SC+UR	40.00	13.3:13.3:13.3	0.904	134.032

Where, SB= sodium benzoate, SA= sodium acetate, SC= sodium citrate, UR= urea, NM= niacinamide, P4K= PEG 4000, P6K= PEG 6000 and PVP= PVP K 30

Table 8: Equilibrium solubility of piroxicam in different blends containing four water-soluble additives (solubilizers)

S.NO.	Blends of Solubilizers	Total conc. (% w/v)	Ratio	Solubility (% w/v)	Solubility Enhancement Ratio
1.	SB+PVP+P4K+NM	40.00	10:10:10:10	0.923	136.898
2.	SB+PVP+P6K+NM	40.00	10:10:10:10	0.986	146.213
3.	SB+SA+UR+NM	40.00	10:10:10:10	1.163	172.364
4.	SB+SA+UR+SC	40.00	10:10:10:10	0.416	61.668
5.	SB+SA+SC+NM	40.00	10:10:10:10	0.851	126.151
6.	SB+SC+UR+NM	40.00	10:10:10:10	0.945	140.123
7.	SC+SA+UR+NM	40.00	10:10:10:10	0.711	105.373
8.	SC+SA+UR+NM	40.00	10:10:10:10	0.711	105.373

Where, SB= sodium benzoate, SA= sodium acetate, SC= sodium citrate, UR= urea, NM= niacinamide, P4K= PEG 4000, P6K= PEG 6000 and PVP= PVP K 30

Table 9: Equilibrium solubility of piroxicam in different blends of (PVP+P4K+SB) water-soluble additives

S. NO.	Blends of Solubilizers	Total Conc. (%w/v)	Ratio	Solubility (% w/v)	Solubility Enhancement Ratio
1.	PVP+P4K+SB	40.00	10:15:15	1.743	258.342
2.	PVP+P4K+SB	40.00	15:10:15	1.235	183.112
3.	PVP+P4K+SB	40.00	15:15:10	1.187	175.947
4.	PVP+P4K+SB	40.00	5:20:15	1.678	248.670
5.	PVP+P4K+SB	40.00	5:15:20	1.617	239.714

Where, SB= sodium benzoate, SA= sodium acetate, SC= sodium citrate, UR= urea, NM= niacinamide, P4K= PEG 4000, P6K= PEG 6000 and PVP= PVP K 3

PREPARATION OF SOLID DISPERSION OF PIROXICAM BY APPLICATION OF MIXED-SOLVECY CONCEPT

For preparation of solid dispersion in 1:4 ratio, accurately weighed 1 gm PVP K 30, 1.5 gm of sodium benzoate and 1.5 gm of PEG 4000 (so that total weight of the mixture was 4 gm)

were taken in a 100 ml beaker and were mixed properly. Then, minimum possible quantity of warm, DM water sufficient to dissolve the above mixture was added, because 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). Dissolution of the water-soluble additives (solubilizers) mixture was facilitated by agitation of a teflon coated magnetic rice bead on a high speed magnetic stirrer. After complete dissolution of solubilizers, 1 gm of piroxicam was dissolved in the above solution and temperature was maintained in the range of 55- 60ºC so as to facilitate the evaporation of water. As evaporation proceeded, 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 wet solid dispersion, thus, obtained was spread on several glass petriplates and these petriplates were kept in hot air dry oven maintained at 50±2ºC so that remaining moisture could also be evaporated easily and a constant weight with no further weight loss (due to evaporation) could be obtained. After complete drying,solid dispersions were crushed using a glass pestle mortar and passed through sieve 40 and were finally stored in an air tight glass bottle.

Table 10: Composition of solid dispersion

S.NO.	Drug:solubilizers Ratio	Quantity taken (gm)			
		Piroxicam	PVP K 30	Sodium Benzoate	PEG 4000
1	1:4	1.00	1.00	1.50	1.50
2	1:6	1.00	1.50	2.25	2.25
3	1:8	1.00	2.00	3.00	3.00
4	1:10	1.00	2.50	3.75	3.00
5	1:12	1.00	3.00	4.50	4.50

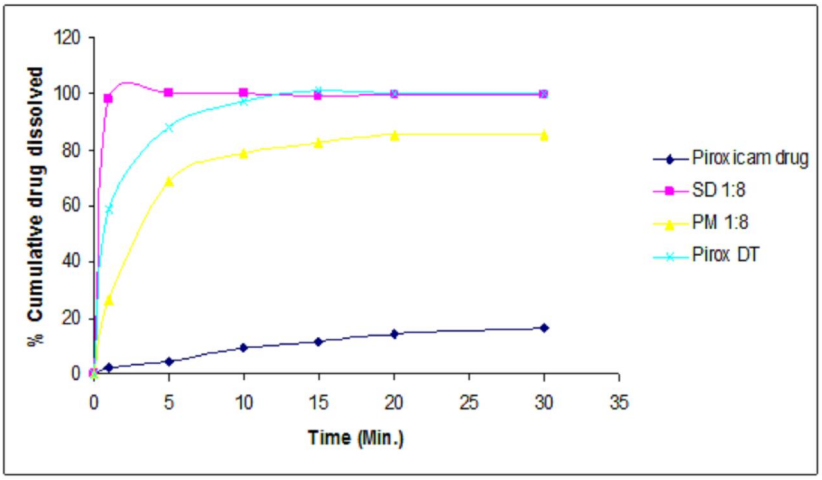
DETERMIATION OF DRUG CONTENT IN SOLID DISPERSIONS AND PHYSICAL MIXTURES

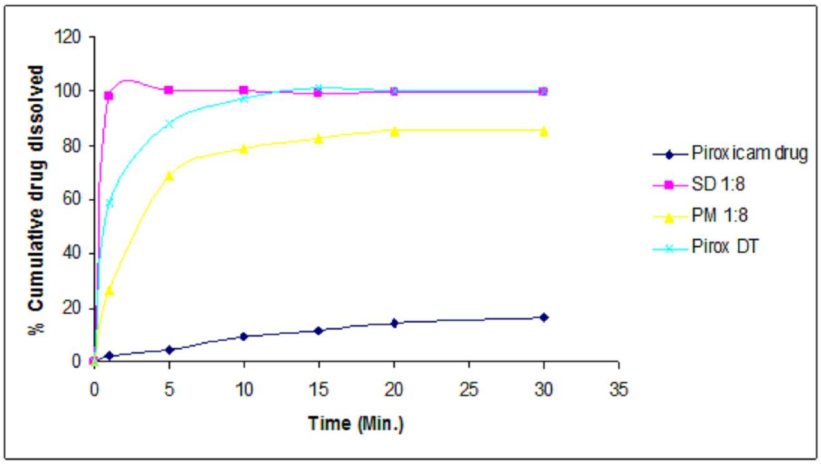
Powered solid dispersion or physical mixture equivalent to 10 mg of piroxicam was accurately weighed and transferred to a 500 ml volumetric flask. About 300 ml of DM water was added and the flask was shaken to dissolve the contents completely and the volume was made upto the mark with demineralized water. The solution was analyzed spectrophotometrically at 358 nm against corresponding reagent blank.

DISSOLUTION RATE STUDIES

Procedure

Solid dispersion or physical mixture equivalent to 10 mg of piroxicam were tested in dissolution rate studies using USP XXIV (type II) dissolution test apparatus (Model TDT6P, Electrolab Mumbai, India) with paddle to rotate at 50 rpm. Nine hundred ml of 0.1 N HCl was taken as dissolution media with temperature of 37± 0.5°C. At definite time intervals, 10 ml of the samples were withdrawn and were analyzed for drug content. Withdrawn samples were also replaced with fresh dissolution media. Calculations for the amount of drug were done using respective regression equations and the results of the dissolution studies are shown from graph.





POWDER X-RAY DIFFRACTION STUDIES

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 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 The powder X-ray diffraction

spectra of piroxicam, prepared solid dispersions and the physical mixtures were obtained using RU-H3R, Horizontal Rotaflex rotating anode X-ray generator instrument, Rigaku (Rigaku International Corporation, Tokyo).

DIFFERETIAL SCANNING CALORIMETRIC STUDIES

Differential scanning calorimetric studies (DSC) and differential thermal analysis (DTA) measure the heat loss or gain resulting from physical or chemical changes within a sample as a function of temperature. Examples of endothermic (heat-absorbing) processes are fusion, boiling, sublimation, vaporization, desolvation, solid-solid.Show in fig.1,2,3.

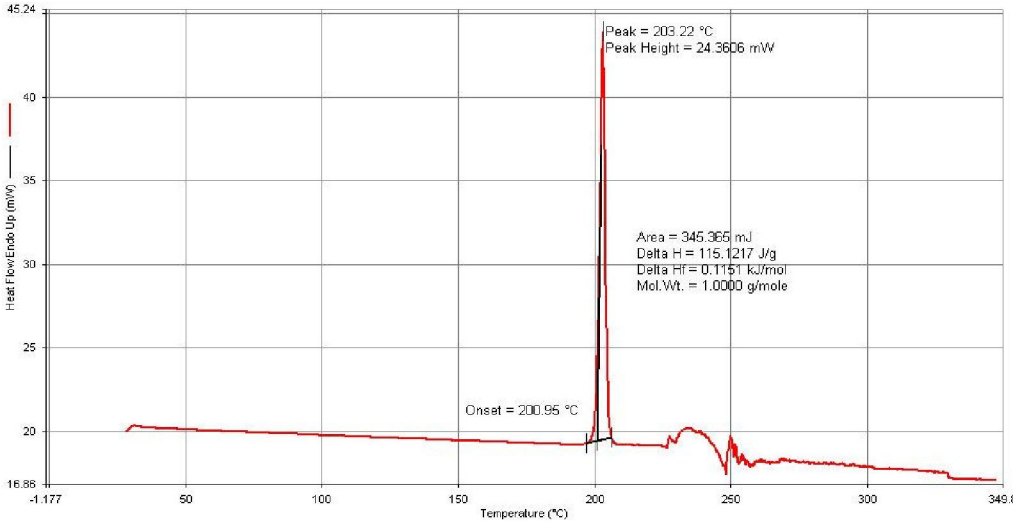


Fig.1: DSC thermogram of piroxicam drug sample

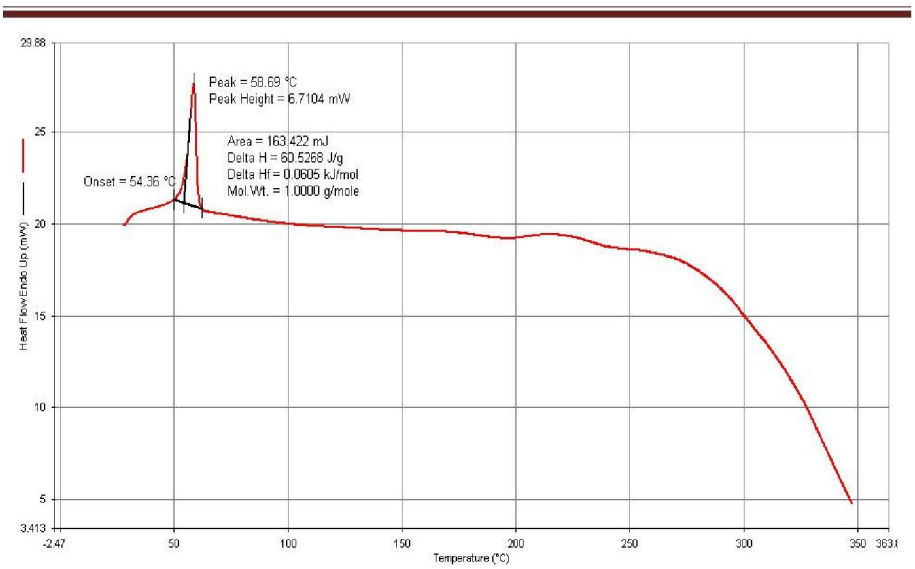
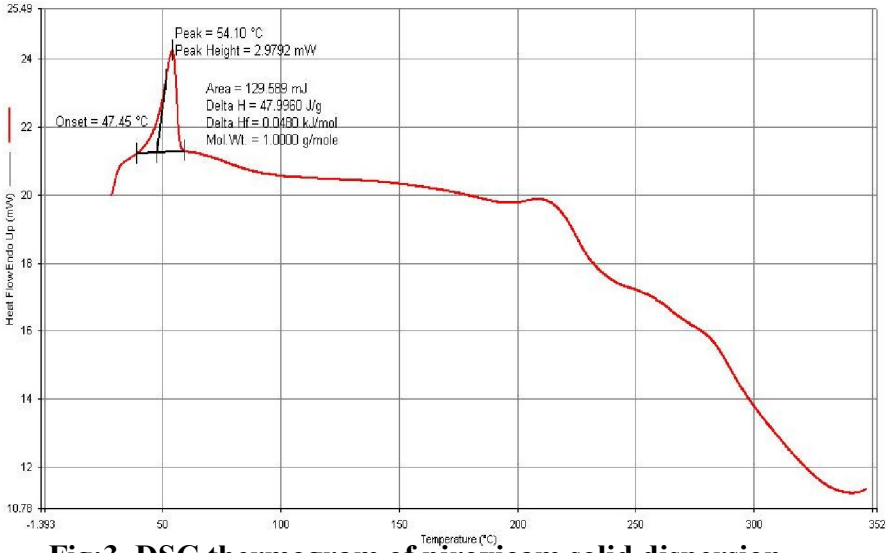


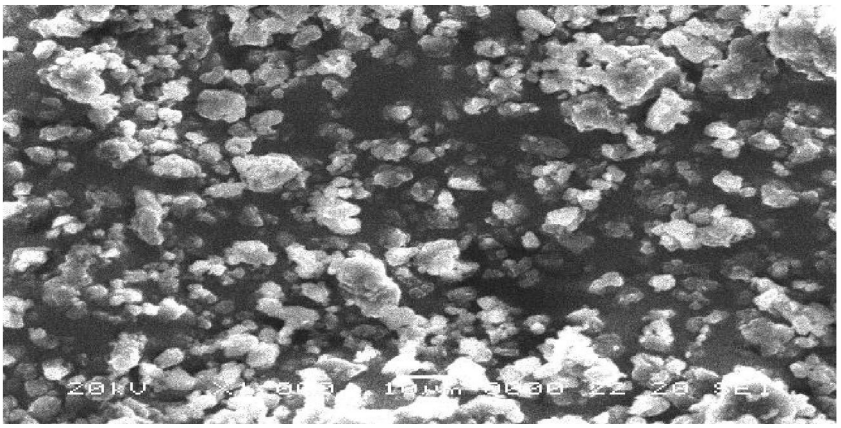
Fig.2 : DSC thermogram of piroxicam physical mixture

SCANNING ELECTRON MICROSCOPY

The scanning electron microscopy is a type of electron microscopy that images the sample surface by scanning it with a high-energy beam of electrons. The electrons interact with the atoms that make up the sample producing signals that contain information about the sample's surface topography, composition and other properties such as electrical conductivity.



Fig;3 DSC thermogram of piroxicam solid dispersion



CHEMICAL STABILITY TESTIG OF SOLID DISPERSION AND PHYSICAL MIXTURE OF DRUGS

Optimized solid dispersions and physical mixtures of drug were subjected to chemical stability testing. Powders of these formulations were kept in 10 ml amber coloured glass vials and vials were plugged and sealed. Vials were kept at room temperature, at 40^0 C and at 55^0 C. The samples were withdrawn at different time intervals and drug contents were determined by UV spectrophotometer. The initial drug content for each formulation was considered as 100.00%.

RESULT AND DISCUSSION

Table:11. Chemical stability data of piroxicam solid dispersions and physical mixture.

Condition	Percent drug residual		
	Time (days)	Solid dispersion 1:8	Physical mixture 1:8
Room Temperature	0	100.00	100.00
	7	99.81	99.69
	15	99.57	99.81
	21	99.22	99.31
	28	98.86	98.81
40^{o}C	0	100.00	100.00
	7	99.75	99.44
	15	99.34	99.06
	21	98.86	98.56
	28	98.38	97.69
55^{o}C	0	100.00	100.00
	7	99.22	99.06
	15	98.15	97.69
	21	97.43	96.82
	28	96.48	95.95

The result of solubility studies shows that. The blend PVP+P4K+SB in the ratio of 10:15:15 shown the highest solubility enhancement, and therefore, this optimized blends of solubilizers was selected for the preparation of solid dispersions.

The result of dissolution studies shows that From the above studies, it is evident that solid dispersions of ratio 1:8 to 1:12 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 and 1:6; and none of the physical mixture dissolved completely even after 30 minutes.

Since, there was significant improvement in dissolution rate when drug:solubilizers were used in 1:8, 1:10 and 1:12 ratio. The dissolution profiles from all three solid dispersions were

almost same. To minimize the quantity of solubilizing agents, 1:8 ratio was considered to be optimum ratio and was used for further studies.

Powder x-ray diffraction Studies showed that the degree of amorphousness in solid dispersion is more.

Differential scanning colorimetric studies showed that, DSC curve of piroxicam showed the peak at 203.22˚ C (at its melting point). In the DSC curves of physical mixture and solid dispersion, the peaks were observed at 58.69˚ C and 54.10˚ C, respectively. These values are very near to the melting point of PEG 4000 (melting point 54˚ C). The reason for one peak may be due to dissolution of sodium benzoate, PVP K 30 and piroxicam in the melted PEG 4000. Since, the DSC curve in case of solid dispersion is very comparable to the DSC curve of physical mixture. Therefore, it is proved that there is no chemical interaction between piroxicam and the solubilizers sodium benzoate, PEG 4000 and PVP K 30.

Scanning electron microscopy (SEM) photographs of pure piroxicam shows characteristic shaped structures, indicating the crystallinity of piroxicam.

Chemical stability studies ,the result showed that the residual drug content after storage for 1 month at different temperature conditions of all formulation was above 90 % (much above 95%), showing very good chemical stabilities at moderate and high temperatures.

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