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Der Pharmacia Lettre, 2010, 2(3):123-135
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ISSN 0975-5071
USA CODEN: DPLEB4

Industry feasible method to improve solubility of Piroxicam with Crospovidone: Preparation, Characterization and tableting consideration

Dinesh Kumar Sharma[1]*, Vipin Bihari Gupta[1] and Suresh Purohit[2]

1.B.R.Nahata College of Pharmacy, Department of Pharmaceutics, Mhow-Neemuch Road, Mandsaur –458001, M.P. India
2. Marwar College of Pharmacy, Jodhpur, India.

Abstract

Nearly 30-45 % of new seeds discovered by recent techniques suffer from poor aqueous solubility. Various techniques, used to enhance the aqueous solubility, are reported to produce many disadvantages. Solid dispersion technique is widely used to enhance aqueous solubility. In spite of consciousness in solid dispersions technique, investigators have been able to provide only few numbers of carriers to the industry. Moreover these carriers are reported to produce many disadvantages. Therefore, definitely there is need to explore such new carriers. Current study was undertaken to explore suitability of one such carrier crospovidone as solubility enhancer. Physical mixtures, kneading mixtures and solid dispersions were prepared by solvent evaporation technique using piroxicam as model drug. Kneading mixtures at drug carrier ratio of 1:7 produced maximum solubility. The resulting systems were subjected to solubility analysis and in vitro dissolution studies, flow properties, X-ray diffraction, Infrared Fourier Transform Spectroscopy (FTIR) and differential scanning calorimetry. Kneading mixtures at 1:7 ratio produced improved flow properties in comparison to pure piroxicam. The % drug dissolved after 5 minutes for PRX: CrosPVP KM 1:7 and pure piroxicam was 26.43 % and 11.49% respectively. 86.57 % of piroxicam was dissolved from PRX: CrosPVP KM 1:7 after 120 minutes. Kneading mixtures were successfully compressed in tablets having all post compression parameters within limit in comparison to tablets prepared using MCC or calcium phosphate as diluent. Lower energy required for dissolution due to change in crystal lattice is responsible for improvement in solubility of drug.

Keywords: Piroxicam, Poorly water soluble drug, Dissolution, Flow properties

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INTRODUCTION

A drug must posses some aqueous solubility for therapeutic efficacy [1]. Recent technologies innovation of combinatorial chemistry and high throughput screening can effectively discover the seeds of new drugs, which present good pharmacological activities. However 35-40 % of these new drugs discovered by those technologies suffer from poor aqueous solubility [2-3]. The solubility/dissolution behavior of a drug is key determinant to its oral bioavailability, the latest frequency being the rate-limiting step to absorption of drugs from the gastrointestinal tract [4-6].
The techniques/approaches that have commonly been used to overcome drawbacks associated with poorly water-soluble drugs, in general includes micronization, salt formation, use of surfactant and use of pro- drug. However all these techniques have potential limitations [7-8].
Solid dispersion (SD) technique has been widely used to improve the dissolution rate, solubility and oral absorption of poorly water-soluble drugs [9-10]. The term solid dispersions have been utilized to describe a family of dosage forms whereby the drug is dispersed in a biologically inert matrix, usually with a view to enhancing oral bioavailability. Chiou and Riegelman defined these systems as the dispersion of one or more active ingredient in an inert carrier matrix at solid state prepared by the melting (fusion), solvent or melting-solvent method [11-13].

Notwithstanding incessant awareness in solid dispersion, very diminutive number of different polymeric carriers has been investigated in past 40 years. In fact majorities of studies have been published so far account on the use of polyethyleneglycol or polyvinypyrrolidone, hydroxypoprylmethylalcohol, polysorbate alone or in combination with polymers or surfactants. Therefore, categorically there is need to investigate new carriers for solubility enhancement [3]. Present study is undertaken to explore one such carrier crospovidone.

Piroxicam was selected for current study. Piroxicam (P, 4-hydroxy-2-methyl-N-(2-piridyl) 2H-1, 2-benzothiazine-3-carboxamide-1, 1-dioxide), a most potent non-steroidal anti-inflammatory and potentially analgesic drug, is an intrinsically interesting chemical molecule. It is used in various acute and chronic musculoskeletal and joint disorders such as ankolysing spondylitis, osteoarthritis and rheumatoid arthritis and in acute gout, dysmenorrhoea and some times for pain associated with inflammation. It belongs to class 2 with a low solubility and high permeability based on the Biopharmaceutics Classification System. It is reported that it takes more than 2 hours to reach the maximum concentration, indicating the slow absorption rate after being administered orally [14-16].

MATERIALS AND METHODS

Piroxicam generously gifted by Asoj Soft Gel, Baroda, India**.** Crospovidone was gifted by Signet Chemical Corporation, Mumbai. All Other ingredients were used as such and were of analytical grade

Preparation of Physical Mixtures (Pm) or Kneading Mixtures (Km) or Solid Dispersions (SD) with Crospovidone (CrosPVP)

Solvent evaporation technique was employed for the preparation of SD of piroxicam (PRX) with the CrosPVP at drug carrier ratios 1: 1, 1:3, 1:5, 1:7 and 1:9. Accurately weighed quantity of the CrosPVP was added to a solution of piroxicam (100mg) in dichlomethane, the solvent was

evaporated at 37 ± 0.5 ^{0} C with constant stirring using magnetic stirrer. Kneading mixtures were prepared by kneading the drug and carrier with approximately 1.5 times their amount of ethanol (90%) for 20 minutes. Physical mixtures were freshly prepared prior to analysis by thoroughly blending the accurately-weighed amount of the drug and selected carrier at above mentioned drug to carrier weight ratios. The resulting systems were subjected to drying in oven till constant weight was achieved at 40 ^{0} C. These systems were pulverized and screened through 100 mesh and were kept in desiccator for further study.

Flow Properties of Drug

Bulk Density and Tapped Density [17]

Bulk density and tapped densities were determined by digital bulk (Dolphin, India) density apparatus. For bulk density determinations, 10ml graduated cylinder containing sample (2.5 gm) was dropped onto a hard base three times and the bulk density was calculated by following formula

$$(D_b) = M/Vo$$

Where, M = mass of powder taken
Vo = unsetteled apparent volume
Db= bulk density

While tapped density was determined by tapping the graduated 10 ml measuring cylinder 100 times. The tapped density was calculated by using following formula

$$\rho_t = M / V_t$$

Where, ρ_t = Tapped density (g/cm^3)
M = Mass of powder (g)
V_t = Tapped volume (cm^3)

Percentage Compressibility [18].

The percentage compressibility was calculated by using following formula

$$\text{Percentage compressibility} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

Hausner's Ratio [18]

The Hausner's ratio was calculated by using following formula

Hausner's ratio = Tapped density / Bulk density

Solubility Analysis

The solubility studies were performed according to a method described by Higuchi and Connors [19]**.** Simulated gastric fluid (SGF) was used for determining the solubility of the resulting systems. A quantity equivalent to 10 mg of drug of resulting systems was added to 5 ml of SGF in a conical flask with screw cap, kept at a shaker and temperature was maintained at 37 ±0.5 ^{0} C

for 24 h. Next morning, the solutions were filtered through 0.45 µm millipore filter and the filtrate was analyzed spectrophotometrically at 334 nm for piroxicam. The results are depicted in table 1.

Table 1: Solubility analysis of resulting systems of piroxicam

Resulting systems of piroxicam weight ratios	Solubility (µg/ml) at 1:1 ratio	Solubility (µg/ml) at 1:3 ratio	Solubility (µg/ml) at 1:5 ratio	Solubility (µg/ml) at 1:7 ratio	Solubility (µg/ml) at 1:9 ratio
KM-PRX-CrosPVP	341.72	352.13	387.01	394.26	334.48
PM-PRX-CrosPVP	316.36	354.35	363.76	386.71	366.78
SD-PRX-CrosPVP	261.11	265.22	269.56	242.69	277.11

PRX: piroxicam CrosPVP-crospovidone, PM-Physical mixture, KM-Kneading mixtures, SD-solid dispersions, pure piroxicam solubility was 179.26(µg/ml)

Dissolution Rate Studies of Resulting Systems and Tablets

Dissolution studies were performed using UPS apparatus I rotating basket for powers and UPS apparatus II rotating paddle for tablets . A quantity equivalent to 20 mg of pure drug or resulting systems or a tablet was added to 900 ml of dissolution medium (SGF) maintained at $37^{0} \pm 0.5^{0}$ C at 100 rpm speed. Three ml of dissolution medium was withdrawn at different time intervals 5, 15, 30, 45, 60, 90 & 120 minutes and filtered through 0.45 µm millipore filter and the filtrate was analyzed spectrophotometrically at 334 nm using SGF (pH 1.2) as blank. Three ml of SGF was added to dissolution medium after every determination to maintain the sink conditions. The experiments were performed in triplicate. The mean concentration of the drug was plotted against time. The results are depicted in fig.1. & 2.

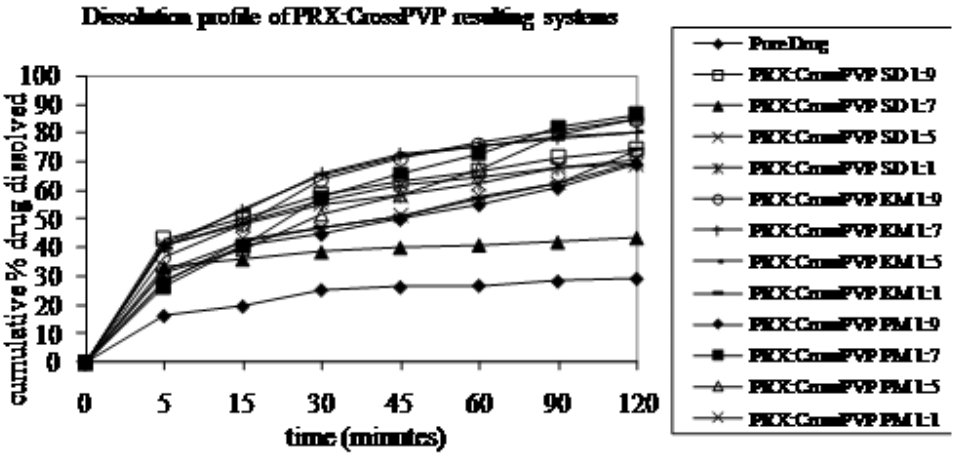

Figure 1 Dissolution profile of piroxicam: crospovidone resulting systems

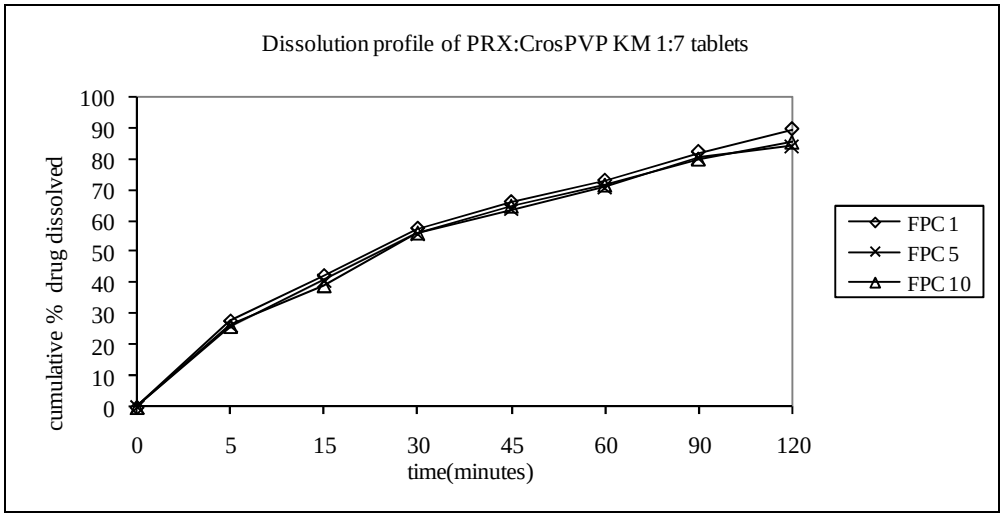

Figure 2 Dissolution profile of PRX: CrosPVP tablets

X-ray Diffraction

X-ray diffraction patterns of the samples were recorded using X-ray diffractometer (Punjab university, India PW3050/60: Goniometer). The experiments were carried out at 25^0 C under the following conditions: voltage 40kV, current 30 mA, 2θ angle with scan step time of 10.33 s with specimen length of 10 mm. The results are depicted in fig. 3 & table 2.

Differential Scanning Calorimetry *(DSC)*

The DSC thermograms were recorded using a differential scanning calorimeter. Approximately 2-5 mg of each sample was heated in an open aluminum pan from 30-300 ^{0} C at a scanning rate of 10 ^{0} C/min under a stream of nitrogen. DSC was performed at S. K. Patel college of Pharmaceutical education, Mehsana, Gujrat, India.

DSC thermograms of selected solid dispersions were obtained on a TA Inst 2000 MTDSC instrument. About 2-3 mg of sample was taken in one of the matched aluminium pan and heated with a continuous purge of argon (44 ml/min). The thermograms recorded for piroxicam & their resulting systems are presented in fig. 4.

FTIR Spectroscopy

The KBr disk sample preparation technique was used to obtain the IR spectra of the samples on an IR spectrophotometer (Shimazdu-FTIR-8400S.). Approximately 100 mg of potassium bromide (spectroscopic grade) was thoroughly mixed with approximately one mg of piroxicam in a glass mortar. The mixture was compressed into transparent disks in a moisture free atmosphere and IR spectra were obtained on a FTIR 8000 spectrophotometer. The scanning range was selected between 4000 and 400 cm^{-1}.The obtained spectra were compared with those reported in official compendia. The FTIR spectra of samples of piroxicam are shown in Fig. 5 Characteristic peaks attributable to

functional groups present in the molecule of drug were assigned to establish the identity (table 3). The study was performed at B.R.Nahata College of pharmacy, Mandsaur, M.P., India.

Formulation of PRX: CrosPVP KM 1:7 tablets

Formulations FPC1 to FPC12 were prepared by using direct compression method. Formulations FPC1 to FPC4 used sodium starch glycolate as variable ingredient at 10, 20, 40, 60 mg respectively to prepare tablets. These tablets were prepared without using any directly compressible diluent The ingredients mentioned in table 4 were mixed and lubricated with talc and magnesium stearate. This blend was compressed to tablets of average weight of 450 mg using eight station rotary tablet punching machine (KMP-8M/C No. 165. Cadmach, Ahmedabad). These tablets used MCC as diluent.

Formulations FPC5 to FPC8 used calcium phosphate instead of MCC as diluent while concentration of sodium starch glycolate was 10, 20, 40 and 60 mg as variable ingredient for FPC5, FPC6, FPC7 and FPC8 respectively.

Formulations FPC9 to FPC12 used only aerosil talc, magnesium stearate, vanillin and neotame without any diluent. Sodium starch glycolate was used at 10, 20, 40 and 60 mg as variable ingredient. Average weight of tablets was kept at 210/225 mg (table 4).

All above preparation contained a quantity equivalent to 20 mg of piroxicam.

Table 4 Formulation of tablets of Piroxicam using PRX: CrosPVP KM 1:7

Ingredients	**Quantity of ingredients/ tablets (mg)**											
	FPC1	FPC2	FPC3	FPC4	**FPC5**	FPC6	FPC7	FPC8	**FPC9**	FPC10	FPC11	FPC12
PRX: CrosPVP KM 1:7	**160**	160	160	160	**160**	160	160	160	**160**	160	160	160
Microcrystalline cellulose	**67**	67	67	67	**-**	-	-	-	**-**	-	-	-
Calcium Phosphate	**-**	-	-	-	**67**	67	67	67	**-**	-	-	-
Mannitol	**171**	161	141	121	**171**	161	141	121	**-**	-	-	-
SSG	**10**	20	40	60	**10**	20	40	60	**10**	20	40	60
Aerosil	**35**	35	35	35	**35**	35	35	35	**33**	23	03	00
Talc	**3**	3	3	3	**3**	3	3	3	**3**	3	3	3
Magnesium stearate	**3**	3	3	3	**3**	3	3	3	**3**	3	3	3
Vannilin	**Q.S**	Q.S	Q.S	Q.S	**Q.S**	Q.S	Q.S	Q.S	**Q.S**	Q.S	Q.S	Q.S
Neotame	**Q.S**	Q.S	Q.S	Q.S	**Q.S**	Q.S	Q.S	Q.S	**Q.S**	Q.S	Q.S	Q.S
Total weight	**450**	450	450	450	**450**	450	450	450	**210**	210	210	225

Evaluation of Tablets

Weight Variation, Tablet Hardness, Friability

Twenty tablets were weighed individually and calculated for average weight of tablet and was presented as mean±sem. Hardness was measured by using a tablet hardness tester (Pfizer Hardness Tester). The test was performed with six tablets. Friability was determined by using Roche friabilator and the percentage friability was determined using following formula

$$\% F = \{(W-W_0)/W\} * 100$$

Where, %F = friability in percent
W = Initial weight of tablet
W_o = weight of tablet after test

Disintegration

For determination of disintegration time a tablet was placed in each of six tubes of basket and through the mechanical device, the basket were raised and lowered in the immersion fluid (water maintained at 37°C). The disintegration time is expressed as mean±sem (table 5).

RESULTS AND DISCUSSION

Solubility Analysis and Dissolution Profile

The solubility analysis results are depicted in table 1. Among all methods, kneading method was reported as most promising method to enhance the solubility of the drug. Kneading mixture at drug carrier ratio 1:7 fashioned maximum solubility of 394.26µg/ml while pure piroxicam was capable to produce solubility of 179.26 µg/ml in SGF (table 1)

Dissolution profile of piroxicam and their resulting systems are depicted in fig. 1 & 2. *In vitro* dissolution profile of all resulting systems produced higher dissolution rates in comparison with pure piroxicam. The % drug dissolved after 5 minutes for PRX: CrosPVP KM 1:7 and pure piroxicam was 26.43 % and 11.49% respectively. 86.57 % of piroxicam was dissolved from PRX: CrosPVP KM 1:7 after 120 minutes.

Flow Properties

Characterization of flow properties is very important parameter to determine suitability of compression properties. The bulk density of piroxicam was found to be 0.297g/ml. Determined Hausner's ratio (1.35) and Carr's index (26.32 %) of piroxicam indicated poor flow characteristic of the drug. (Table 6).

Kneading mixtures prepared with CrosPVP at drug carrier ratio 1:7 were found to have Hausner's ratio and % compressibility of 1.16 and 14.34 % respectively indicating good flow properties.

On the basis of solubility analysis and dissolution profile PRX: CrosPVP KM 1:7 were selected for further characterization and subjected to X-ray diffraction, Differential scanning calorimetry and FTIR studies.

XRD Studies

X-ray diffraction of piroxicam displayed four major peaks marked as 1, 2, 3 and 4 at 2θ : 8.62 (4273), 14.51 (5088), 17.71 (7978), 27.41(8552). These four major peaks of piroxicam in kneading mixtures of piroxicam with CrosPVP at 1:7 ratio were reduced to 87 %, 88 %, 87 % and 86 % intensity respectively (Fig. 3 & table 2)

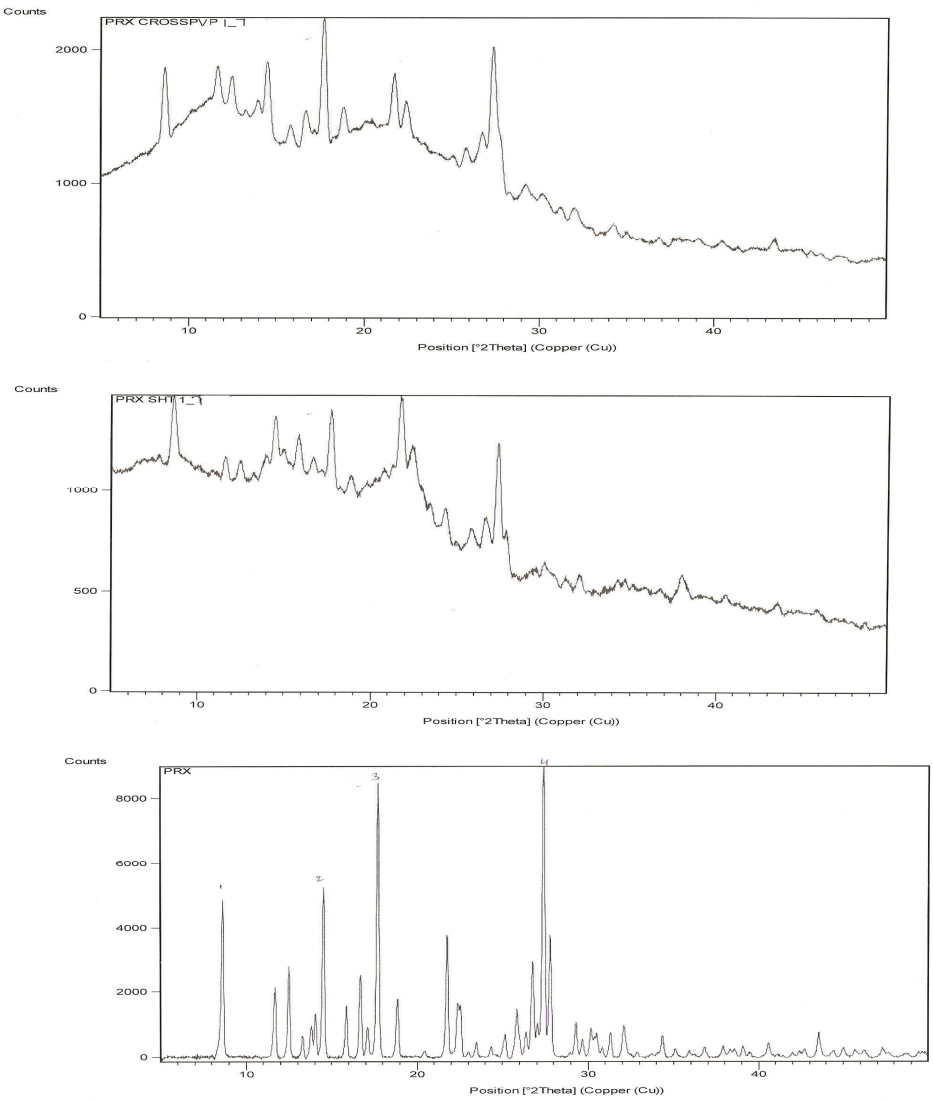

Figure 3 XRD of (from bottom to top)PRX, PRX: CrosPVP KM 1: 7, CrosPVP

Table 2 XRD results and % reduction of intensity of peaks for piroxicam and corresponding systems

S.No.	Major Peaks Piroxicam	Major Peaks PRX: CrosPVP: KM 1:7	% reduction of intensity of peaks
1.	8.62(4273)	8.62(521)	87.80
2.	14.51(5088)	14.5(579)	88.62
3.	17.71(7978)	17.68(1020)	87.21
4.	27.41(8552)	27.35(1165)	86.37

Differential Scanning Calorimetry

As apparent from the figure 4, piroxicam has a sharp melting endotherm at 204.67 ^{0} C. Cross PVP has melting at 96.96 ^{0}C. However, drug melting endotherm for piroxicam in PRX: CrosPVP KM 1:7 was observed but it was slightly shifted to 201.17^0 C and an additional endotherm was also observed at 229.87 ^{0} C indicating that drug was changed to different form. Present results in association with prominent lessening in peaks in X-ray diffraction suggest formation of amorphous forms or change of different crystal lattice. (the results are shown in fig.4)

FTIR of Piroxicam and PRX: CrosPVP KM 1:7

FTIR spectra of Piroxicam reported characteristic peaks of aromatic C-H stretching, aromatic C-H bending, C-S stretching, C=O stretching, C=C, C=N ring stretching, asymmetric $S(=O)_2$ stretching, symmetric $S(=O)_2$ stretching, secondary amine N-H stretching and OH stretching at 3022, 877, 690, 1741, 1527, 1348, 1149, 3338 and 3645 respectively.

CrosPVP KM 1:7 reported absence of characteristic peaks for OH stretching in range 3650-3584 indicating formation of different crystal lattice which is further confirmed in DSC and XRD results. While all other characteristic peaks were obverted with insignificant changes. (fig. 5 & table 3)

Table 3 Functional groups and corresponding IR peaks of piroxicam

Group	Reported Values	Observed Values for PRX	PRX:CrosPVP KM 1:7
Aromatic C-H stretching	3100-3000	3022	2962
Aromatic C-H bending	900-675	877	837
C-S, stretching	700-600	690	633
C=O stretching	1870-1540	1741	1647
C=C, C=N ring stretching	1600-1430	1527	1531
Asymmetric $S(=O)_2$ stretching	1350-1430	1348	1359
Symmetric $S(=O)_2$ stretching	1160-1120	1149	1168
Secondary amine N-H stretching	3350-3310	3338	3338
OH stretching	3650-3584	3645	Absent

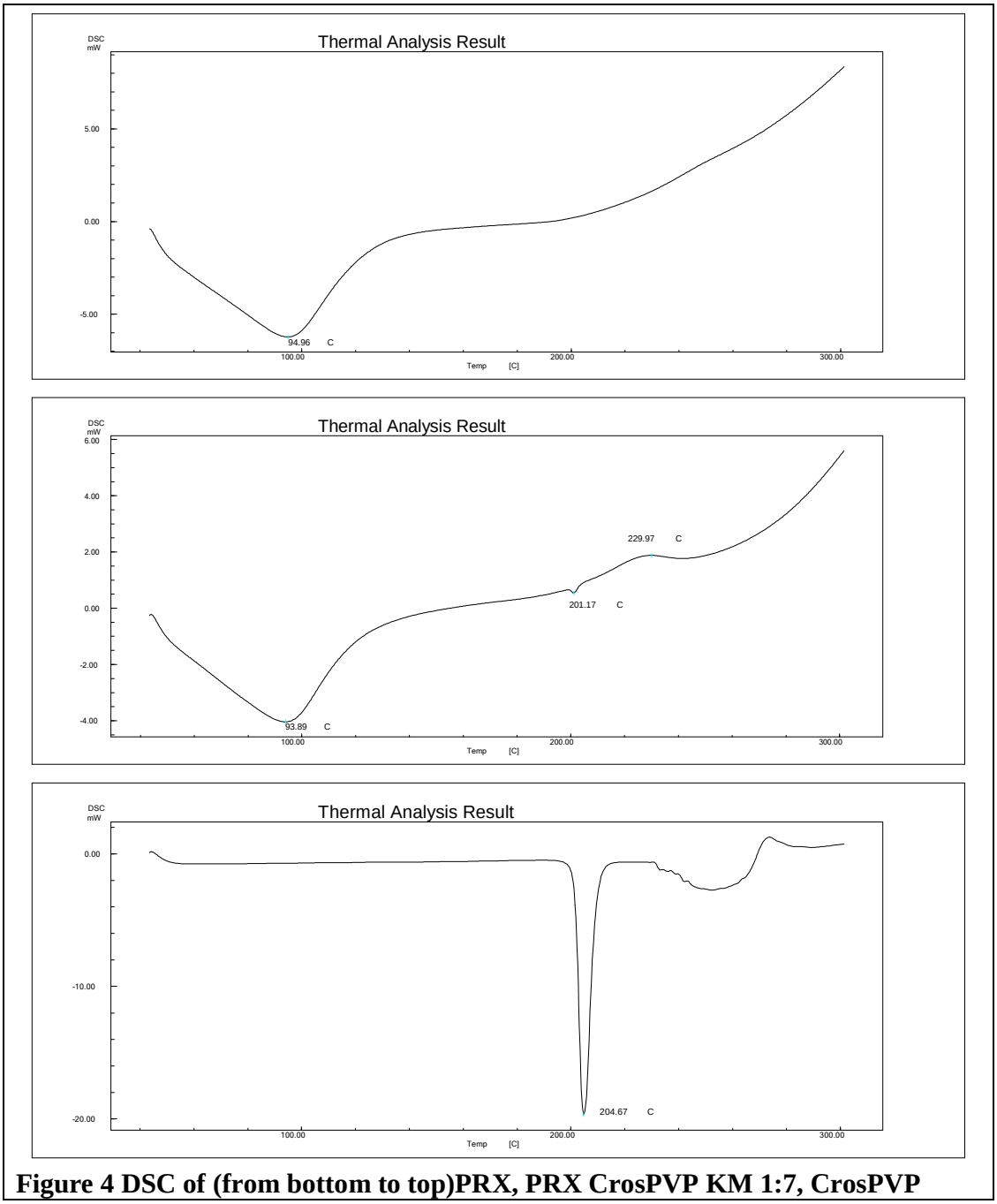

Figure 4 DSC of (from bottom to top)PRX, PRX CrosPVP KM 1:7, CrosPVP

Evaluation of the Prepared Tablets

The prepared tablets were evaluated for different post compression parameters like hardness, weight variation, friability, thickness, drug content and disintegration.

Evaluation of PRX: CrosPVP KM 1:7 Tablets:

All the prepared formulations showed good hardness ranging from 2.6±0.1 to 3.6±0.24 Kg/cm^2 indicating good mechanical strength to tolerate the mechanical stress during handling and transportation. While tablets prepared without MCC or calcium phosphate showed lower hardness attributed to absence of any directly compressible material.

Disintegration of all tablets was ranging from 14.0±0.25 to 46.17±0.47 seconds. Weight variation, friability, thickness and drug content were also found within the limits for all preparations (Table 5).

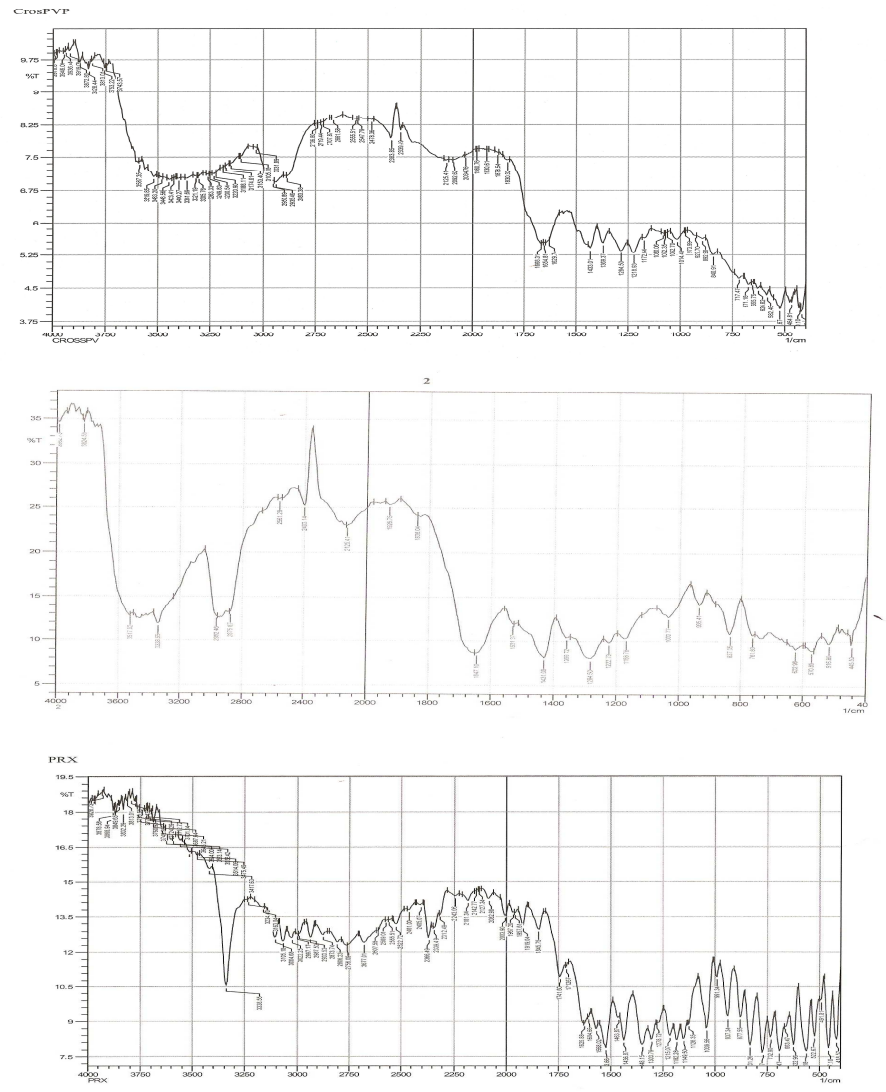

Figure 5 FTIR of (from bottom to top) PRX, PRX: CrosPVP KM 1: 7, CrosPVP

Table 5 Evaluation of PRX: CrosPVP KM 1:7 tablets

Evaluation parameters	Formulation codes					
	Hardness[a]	Weight variation[d]	Friability[a]	Thickness[c] (mm)	Drug Content[b]	Disintegration[a]
FPC1	**3.1±0.24**	**102.9±0.47**	**0.771±0.03**	**3.75±0.09**	**99.5±0.27**	**16.17±0.47**
FPC2	2.9±0.1	103.5±0.31	0.65±0.05	3.16±0.06	99.7±0.15	15.67±0.33
FPC3	2.7±0.122	102.0±0.27	0.717±0.07	3.67±0.04	99.4±0.01	15.83±0.40
FPC4	2.6±0.1	102.2±0.23	0.81±0.035	3.60±0.04	99.7±0.08	16.0±0.44
FPC5	**3.6±0.24**	**103.9±0.17**	**0.808±0.03**	**3.72±0.05**	**99.7±0.05**	**15.33±0.84**
FPC6	3.2±0.2	104.5±0.19	0.840±0.02	3.55±0.06	99.6±0.14	15.0±0.36
FPC7	3.1±0.24	103.7±0.19	0.847±0.01	3.38±0.05	99.8±0.43	14.0±0.25
FPC8	3.0±0.00	103.8±0.19	0.691±0.04	3.51±0.06	99.7±0.03	15.33±0.33
FPC9	2.3±0.21	101.3±0.13	0.717±0.04	3.35±0.02	99.6±0.12	67.5±0.5
FPC10	**2.5±0.21**	**99.0±0.15**	**0.831±0.01**	**3.39±0.01**	**99.8±0.05**	**22.5±0.61**
FPC11	2.2±0.16	101.3±0.14	0.851±0.01	3.36±0.01	99.8±0.05	39.00±1.46
FPC12	2.6±0.24	102.3±0.13	0.802±0.01	3.32±0.03	99.7±0.05	46.17±0.477

[a] indicates mean± sem of six tablets; [b] indicates mean± sem of three tablets; [c] indicates mean± sem of ten tablets; [d] indicates mean± sem of twenty tablets

Table 6 Flow properties of piroxicam and its corresponding systems

Drugs	**Bulk density** g/ml	**Tapped density** g/ml	**Hausner's ratio)**	**Carr's Index/ % compressibility**
Piroxicam	0.297	0.40	1.35	26.32
PRX:CrosPVP alone	0.132	0.163	1.16	14.34
PRX: CrosPVP with MCC	0.157	0.232	1.38	30.12
PRX: CrosPVP with Calcium phosphate	0.146	0.221	1.18	29.19

The values represent average of three determinants

FPC 1 (containing only kneading mixtures), FPC 5 (containing MCC in addition to kneading mixtures) and FPC 10 (containing calcium phosphate in addition to kneading mixtures) for piroxicam produced desirable post compression parameters. The FPC 1, FPC 5 and FPC 10 formulations were studied for *in vitro* dissolution profiles also. *In vitro* dissolution profiles and post compression parameters of FPC 1 (containing only kneading mixtures) were comparable to FPC 5 and FPC 10. Thus studies propose the usefulness of crospovidone as solubility enhancer to enhance the solubility of piroxicam. Further tablets prepared using crospovidone also suggested promising application of the carrier in improving tableting properties of poorly water soluble drugs (table 5).

CONCLUSION

Crospovidone successfully improved the solubility and *in vitro* dissolution for piroxicam in kneading mixtures at drug carrier ratio 1:7. This improvement *in vitro* dissolution is expected due to of amorphous form revealed by X-ray diffraction and DCS studies. Moreover, crospovidone is widely used in pharmaceutical industry and is also reported to enhance solubility.

REFERENCES

[1] HC Ansel, LV Allen, CG Popovich. Pharmaceutical dosage forms and drug delivery systems, 7th Edn, Lippincott Williams and Wilkins, **2000**; pp.60-61,66
[2] T Ohara; S Kitamura; T Kitagawa ; K Terada. *Int. J. Pharm*, **2005**, 302, 95-102.
[3] G V den Mooter; I Weuts; T D Rider; N Blaton. *Int. J. Pharm*, **2006**, 316,1-6
[4] J Hecq; M Deleers; D Fanara; H Vranckx ; K Amighi. *Int. J. Pharm*, **2005**, 299, 167-177
[5] S G Kapsi ; J W Ayres. *Int. J. Pharm*, **2001**, 299,193-203
[6] I Orienti; F Bigucci; B Luppi; T Cerchiara; G Zuccari; P Giunchedi ; V Zecchi. *Int. J. Pharm*, **2002**, 54,229-233
[7] S Patro; K Himasankar; A A Choudhury; M E B Rao. *Indian J. Pharm. Sci*, **2005**, 67(3),334-341.
[8] AS Omaima; AH Mohammed; AM Nagia ; SZ Ahmed. *AAPS PharmSciTech*, **2006**, 7(2), E1-E9.
[9] N Tanaka; K Imai; K Okimoto; S Ueda; YT Rinta Ibuki; K Higaki ; T Kimura. *Journal of controlled release*, **2006**, 122, 51-56.
[10] Q M C Duncan. *Int. J. Pharm*, **2002**, 231, 131-144.
[11] Hayes, Davis, Morella and Angelo Mario. United States Patent. No. 6881745, **2005.**
[12] Debjit Bhowmik; Chiranjib. B; Jitendra Yadav; R. M. Chandira; K. P. Sampath Kumar. *Der Pharmacia Lettre*, **2010**, 2, 1, 495-504.
[13] Anshu Sharma; C. P. Jain. *Der Pharmacia Lettre*, **2010**, 2, 2, 54-63.
[14] A Bertoluzza ; M Rossi; P Taddei; E Redenti; Zanol M; Ventura P.J. *Molecular science*, **1999**, 480-481, 535-539.
[15] Y Javadzadeh; MR Siahi-Shadbad; M Barzergar-Jalali; A Nokhodechi. *II Famaco*, **2005**, 60, 361-365.
[16] HS Gwak; JS Choi; HK Choi. *Int. J Pharm*, **2005**, 297, 156-161.
[17] Lachman, L, Liberman, H.A. Theory and Practice of Industrial Pharmacy; 3rd ed. Varghese Publication House , Hind Rajasthan Building Dadar, Bombay **1990**;293-294, 329-335.
[18] Aulton ME. Pharmaceutics the Science of Dosage Form Design, 2nd ed. Churchill Livingstone, New York ,**2004;** pp. 66.
[19] T Higuchi , KA Connors. *Instrum*,**1995**,4,117-210.