Int. J. Chem. Sci.: 10(1), 2012, 399-412
ISSN 0972-768X
www.sadgurupublications.com

FORMULATION AND *IN VITRO* EVALUATION OF BUCCAL TABLETS OF PIROXICAM

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ABSTRACT

Buccoadhesive tablets of piroxicam were prepared by using HPMC K4M and carbopol 934 as mucoadhesive polymers. Ten formulations were developed with varying concentrations of polymers. H1 to H5 formulations were composed of HPMC K4M in ratios of 1 : 1 to 1 : 5 whereas in C1 to C5 formulations carbopol 934 was used in ratios of 1 : 0.25 to 1 : 1.5. The formulations were tested for *in vitro* drug release, *in vitro* bioadhesion, moisture absorption, *in vitro* retention time and *in vitro* drug permeation through porcine buccal mucosa. Formulation H3 showed maximum release of the drug (97.67 ± 0.41) with the peppas model release profile and permeated 26.52 ± 0.19 of the drug through porcine buccal membrane. H3 formulation showed 12.5 g of mucoadhesive strength. FTIR results showed no evidence of interaction between the drug and polymers. The results indicate that suitable bioadhesive buccal tablets with desired permeability could be prepared.

Key words: Piroxicam, Buccal tablets, Formulation, Evaluation.

INTRODUCTION

The oral cavity is an attractive site for the administration (delivery) of drugs because of ease of administration. Various dosage forms like tablets, capsules and liquid preparations are administered by this route. There is a possibility for mucosal (local effect) and transmucosal (systemic effect) drug administration. In first case, the mucosal administration of drugs is to achieve site-specific release of drug on the mucosa, whereas, in second case, transmucosal administration involves drug absorption through mucosal barrier to reach the systemic circulation[1,2]. Among the various transmucosal routes like nasal, rectal, vaginal, ocular, pulmonary and buccal routes[3,4], the buccal mucosa is an attractive alternative to the oral route of drug of administration and it is a potential site for the delivery of drugs to the systemic circulation[5]. A drug administered through buccal mucosa enters directly to the

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systemic circulation and there by bypassing the first-pass hepatic metabolism, gastric irritation and other problems associated with conventional oral route. Among these the buccal mucosa has several advantages like excellent accessibility, an expanse of smooth muscle and immobile mucosa, moderate permeability, less enzymatic activity and suitable for the administration of retentive dosage forms[6-8]. Moreover, buccal drug absorption can be promptly terminated in case of toxicity by removing the dosage form from the buccal cavity. It is also possible to administer drugs to patients who cannot be dosed orally to prevent accidental swallowing[9]. Therefore adhesive mucosal dosage forms were suggested for oral delivery, which includes adhesive tablets, adhesive gels and adhesive patches. So, buccal route is an attractive site for administration of drugs. These buccal tablets are small, flat and are intended to be held between the cheek and teeth or in the cheek pouch[10]. Piroxicam is a non-steroidal anti-inflammatory (NSAID) drug and it is a non selective cyclooxigenase (COX) inhibitor used in the treatment of rheumatoid arthritis and osteoarthritis. It also possesses analgesic and antipyretic properties. Piroxicam was selected as a model drug for the investigation because to avoid high gastric irritation (when given orally). A suitable buccal drug delivery system should possess good bioadhesive properties, so that it can retain in the oral cavity for the desired duration. In addition, it should release the drug in a predictable manner to elicit the required therapeutic response[11]. In this investigation, buccoadhesive tablets of Piroxicam have been developed using bioadhesive polymers like hydroxy propyl methyl cellulose K4M (KPMC K4M, Non-ionic polymer) and carbopol 934 (anionic nature), each formulation with different drug: polymer ratio. The main objective of this investigation is to avoid gastric irritation (when given orally) and to study the effect of drug: polymer ratio on *in vitro* drug release and other bioadhesive properties.

EXPERIMENTAL

Material and methods

Piroxicam was donated by Dynamed Pharmaceuticals, Hyderabad. Hydroxy propyl methyl cellulose (HPMC K4M) was donated by Zydus Cadila, Ahmedabad and carbopol 934 was purchased from Himedia Laboratories. Mannitol was purchased from Universal Laboratories. All other chemicals and reagents used were of analytical reagent grade and purchased from Himedia, Hyderabad.

Bioadhesive tablets preparation

Piroxicam was mixed manually in poly bags with different ratios of hydroxy propyl methylcellulose K4M (HPMC K4M) and carbopol 934 as mucoadhesive polymers and mannitol as diluents for 10 min. The blend was lubricated with magnesium stearate for 3-5 min and then compressed into tablets by direct compression method using 8 mm diameter

punches in a sixteen station rotary tablet-punching machine (Cadmach, Ahmedabad, India). Compositions of buccal adhesive tablet formulations are given in Table 1. Each tablet (200 mg) contained 20 mg of piroxicam. The mass of the tablets was determined using a digital balance (Shimadzu) and thickness with digital vernier calipers (Mitutoyo).

Table 1: Composition of Piroxicam buccal tablets

Formulation	D : P	Drug	HPMC K4M	Carbopol 934	Mannitol	Mg sterate
H1	1 : 1	20 mg	20 mg	-	156 mg	4 mg
H2	1 : 2	20 mg	40 mg	-	136 mg	4 mg
H3	1 : 3	20 mg	60 mg	-	116 mg	4 mg
H4	1 : 4	20 mg	80 mg	-	96 mg	4 mg
H5	1 : 5	20 mg	100 mg	-	76 mg	4 mg
C1	1 : 0.25	20 mg	-	5 mg	171 mg	4 mg
C2	1 : 0.5	20 mg	-	10 mg	166 mg	4 mg
C3	1 : 0.75	20 mg	-	15 mg	161 mg	4 mg
C4	1 : 1	20 mg	-	20 mg	156 mg	4 mg
C5	1 : 1.25	20 mg	-	25 mg	151 mg	4 mg

Assay of piroxicam

Three tablets were taken and powdered; powder equivalent to one tablet was taken and dissolved in 100 mL of pH 7.4 phosphate buffer on a rotary shaker overnight. The solution was centrifuged and the supernatant was collected. The absorbance was measured by using UV-Visible Spectrophotometer (Shimadzu) at 242 nm.

In vitro release studies

The drug release from buccal tablets was studied by using USP type II (paddle type) dissolution test apparatus. Tablets were supposed to release the drug from one side only; therefore an impermeable backing membrane was placed one side of the tablet. The tablet was further fixed to a 2 × 2 cm glass slide with a solution of cyano acrylate adhesive. Then it was placed in the dissolution apparatus containing 500 mL of pH 7.4 phosphate buffers and paddle was rotated at 50 rpm at a temperature of 37 ± 0.5^{o}C. Samples of 5 mL were collected at different time intervals up to 8 hrs and analyzed spectrophotometrically at 242 nm.

Tissue isolation

Porcine buccal tissue from domestic pigs was obtained from a local slaughterhouse and used within 2 h of slaughter. The tissue was stored in pH 6.6 phosphate buffer at 4^{o}C after collection. The epithelium was separated from the underlying connective tissue with a surgical technique and the membrane was allowed to equilibrate for one hour in receptor buffer to regain lost elasticity.

In vitro bioadhesion study

Mucoadhesive strength of piroxicam buccal tablets with porcine buccal mucosa was measured using a modified 2-arm balance[12,13]. Porcine buccal mucosa obtained from a local slaughterhouse and stored in pH 6.6 phosphate buffer at 4^{o}C upon collection. The experiment was performed within 3 h of procurement of the mucosa. The porcine buccal mucosa was fixed to the stainless steel piece with cyanoacrylate adhesive and placed in a beaker; then pH 6.6 phosphate buffer was added into the beaker up to the upper surface of the porcine buccal mucosa to maintain buccal mucosal viability during the experiment. Then the tablet was attached to the upper clamp of the apparatus and the beaker was raised slowly to establish contact between porcine buccal mucosa and the tablet.

A preload of 50 g was placed on the clamp for 10 min to establish adhesive bond between the tablet and porcine buccal mucosa. After completion of preload time, preload was removed from the clamp and water was added into the beaker from burette at a constant rate. The addition of water was stopped when tablet was detached from porcine buccal mucosa. The weight of water required to detach the tablet from porcine buccal mucosa was noted as mucoadhesive strength and experiment was repeated with fresh mucosa in an identical manner.

In vitro retention time

The *in vitro* retention time is one of the important physical parameter of buccal mucoadhesive tablet. The adhesive tablet was pressed over pig mucosa for 30 s and secured on glass slab and was immersed in a basket of the dissolution apparatus containing 750 mL of pH 7.4 phosphate buffer, at 37^{o}C. The paddle was adjusted at a distance of 5 cm from the tablet and rotated at 25 rpm. The time for complete erosion or detachment of tablet from the porcine buccal mucosa was recorded as *in vitro* retention time.

Moisture absorption test

Agar (5% w/v) was dissolved in hot water. It was transferred into Petri dishes and allowed to solidify. Six buccal tablets (pre weighed) from each formulation were placed in a

vacuum oven overnight to remove moisture and laminated on one side with a water impermeable backing membrane. Then they were placed on the surface of the agar and incubated at 37^{o}C for one hour. Then the tablets were removed and weighed and the percentage of moisture absorption was calculated by using following formula:

$$\% \text{ Moisture absorption} = [(\text{Final weight} - \text{Initial weight}) / \text{Initial weight}] \times 100$$

Surface pH

The buccal tablets were placed in boiling tubes and allowed to swell in contact with pH 7.4 phosphate buffer (12 mL). Thereafter, surface pH measurements at predetermined intervals of 0.25, 0.5, 0.75, 1, 2, 3, 4, 5, 6, 7 and 8 h were recorded with the aid of a digital pH meter. These measurements were conducted by bringing a glass microelectrode to the surface of the tablets and allowing it to equilibrate for 1 min prior to recording the readings. The experiment was performed in triplicate.

In vitro drug permeation through porcine buccal membrane

In vitro permeation of piroxicam from matrix tablets through the porcine buccal membrane was studied. The test was carried out in the standard Franz diffusion cell with a diffusion area of 30.02 cm^2 and the acceptor compartment volume of 21 mL. A semi permeable membrane (porcine buccal mucosa) was clamped between the donor and acceptor compartments. The phosphate buffer (37^{o}C) in the acceptor compartment was continuously stirred at 600 rpm using a magnetic stirrer. The tablet was placed into the donor compartment and was wetted with 1 mL of phosphate buffer. The amount of drug permeated through the membrane was determined by removing aliquots from the receptor compartment and by replacing the same volume of buffer. The piroxicam flux through the membrane was calculated using the equation:

$$J = dQ / A\,dt$$

Where, J is the steady-state flux

dQ is the amount of drug substance permeated through the membrane

A is the diffusion area.

dt is the time of exposure

Characterization of drug in buccal tablets

FTIR and DSC studies were conducted for characterization of drug in tablets of selected optimized formulation (H3). The buccoadhesive tablets were compressed and

powdered. The pelletized powder along with KBr was used for FTIR studies. The IR spectra were recorded using Fourier Transform Infrared spectrophotometer. The IR spectrum of pure piroxicam and pelletized powder of tablets were taken, interpreted and compared with each other. Thermograms of pure piroxicam and powder sample of tablets were taken from DSC study. An empty aluminum pan was used as a reference. DSC measurements were performed at a heating rate from 50 to 400ºC using aluminum sealed pan. The sample size was 3.532 mg for pure drug and 5.477 mg for powder sample of tablets in measurements. During the measurement, the sample cell was purged with nitrogen gas.

RESULTS AND DISCUSSION

Mass, thickness and drug uniformity

The weight variation and the thickness of the tablets (Table 2) were within the limits of uniformity. The mass ranged from 199.85 to 200.74 mg with SD values 0.52-1.01. Thickness ranged between 3.51 and 3.55 mm with SD values of 0.5 to 1.2. The drug content was 99.81 ± 0.44% in formulation H1, 98.96 ± 0.44 in formulation H5, 98.77 ± 0.92 in formulation C1 to 100.28 ± 0.57 in formulation C5 and the friability ranged from 0.58 to 0.91. The hardness of all prepared tablets was in the range of 3.5 to 4 Kg.

Table 2: Mass, thickness, friability and drug content

Formulation	Mass (mg)[a]	Thickness (mm)[a]	Friability (%)[a]	Assay (%)[b]
H1	200.74 ± 0.61	3.55 ± 0.03	0.75	99.81 ± 0.44
H2	200.04 ± 0.80	3.55 ± 0.02	0.83	99.15 ± 0.75
H3	200.38 ± 0.71	3.54 ± 0.03	0.66	99.53 ± 0.92
H4	200.42 ± 0.75	3.55 ± 0.02	0.58	98.77 ± 1.00
H5	200.45 ± 0.64	3.55 ± 0.02	0.67	98.96 ± 0.44
C1	199.91 ± 1.01	3.51 ± 0.02	0.91	98.77 ± 0.92
C2	199.98 ± 0.82	3.52 ± 0.01	0.66	99.81 ± 0.72
C3	199.99 ± 0.92	3.52 ± 0.02	0.66	99.43 ± 0.28
C4	199.85 ± 0.87	3.51 ± 0.02	0.67	100.28 ± 0.49
C5	200.33 ± 0.52	3.52 ± 0.02	0.75	100.28 ± 0.57

Mean ± SD; [a] n = 10, [b] n = 3

In vitro drug release studies

The release of piroxicam from buccoadhesive tablets was varied according to the type and ratio of matrix forming polymers. The most important factor affecting the rate of release from the buccal tablets is the drug: polymer ratio. Release rates slowed down when the concentration of HPMC K4M and carbopol 934 increased from 1 : 1 to 1 : 5 ratios (Fig. 1) and 1 : 0.25 to 1 : 1.50 (Fig. 2) respectively. This is because as the proportion of these polymers in the matrix increased, there was an increase in the amount of water uptake and proportionally greater swelling leading to a thicker gel layer.

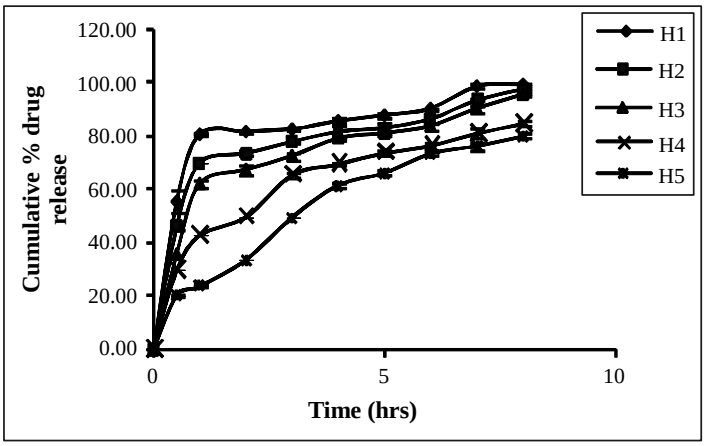

Fig. 1: Drug release profile of piroxicam buccal tablets formulated with HPMC K4M (Mean ± SD, n = 3)

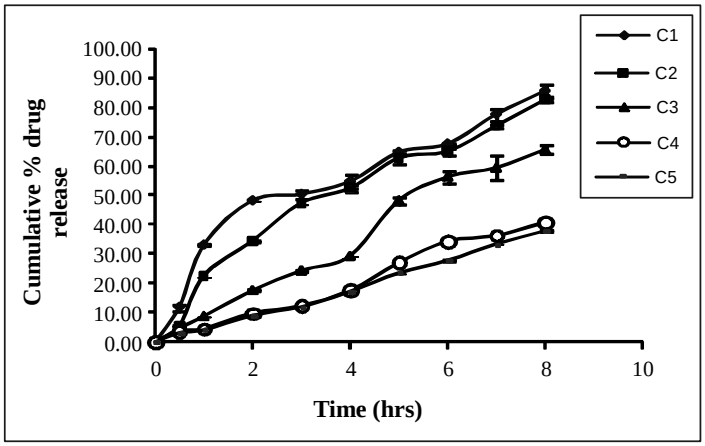

Fig. 2: Drug release profile of piroxicam buccal tablets formulated with carbopol 934 (Mean ± SD, n = 3)

When the higher R^2 values for first-order and zero order are considered, the release data of formulations H1, H2, H3, H4, H5, C1 and C2 were fit better with the first order kinetics, where as the release data of formulations C3 to C5 seemed to fit better with zero order kinetics. Therefore the release rate in formulations H1, H2, H3, H4, H5, C1 and C2 were dependent of concentration or amount of drug incorporated, where as in formulations C3 to C5, it is independent.

When the higher R^2 values of Higuchi model, Korsemeyer-peppas and Hixson-crowel model are considered in the release data of formulations H3, H5, C1 and C2 were seem to fit better with the Higuchi model i.e. the release mechanism is Fickian diffusion. The release data of formulations H1, H2, H4 and C3 seem to fit better with the Korsemeyer-peppas model i.e. the drug release mechanism depends on the value of release exponent (n), the release data of formulations C4 and C5 seem to fit better with Hixson-crowel model i.e. the release mechanism is erosion. As the n values of H1, H2 and H4 were less than 0.5, the drug release mechanism of these formulations is Fickian diffusion, where as the drug release mechanism from C3 is anomalous or non- Fickian diffusion, because the 'n' value for this formulation is in between 0.5 to 1 (Table. 3).

Table 3: Kinetic data of formulations

Formulation	Zero order (R^2)	First order (R^2)	Higuchi (R^2)	Peppas		Hixson-crowel (R^2)
				(R^2)	n	
H1	0.5398	0.8117	0.7681	0.828	0.16	0.8281
H2	0.6351	0.8788	0.8481	0.8966	0.22	0.8643
H3	0.7134	0.9741	0.9043	0.9028	0.29	0.8964
H4	0.813	0.9616	0.9667	0.9819	0.36	0.9242
H5	0.9287	0.9903	0.9862	0.9747	0.54	0.9776
C1	0.9001	0.9537	0.9741	0.9115	0.60	0.9564
C2	0.9491	0.9794	0.9779	0.9231	0.86	0.984
C3	0.9832	0.9728	0.9145	0.9917	0.97	0.9791
C4	0.9837	0.9759	0.893	0.9669	0.93	0.9792
C5	0.9954	0.9866	0.9039	0.981	0.95	0.9904

In vitro mucoadhesive strength measurement

The results of the bioadhesion strength of piroxicam buccal tablets are given in Table 4. In all the formulations, as the polymer concentration increased, the mucoadhesive

strength increased. Buccal tablets formulated with carbopol 934 showed stronger mucoadhesion than HPMC K4M formulations. Very strong bioadhesion could damage the epithelial lining of the buccal mucosa.

Table 4: *In vitro* mucoadhesive strength, moisture absorption, *in vitro* residence time

Formulation	Mucoadhesive strength (g)[a]	% moisture absorbed[a]	*In vitro* retention time (hrs)[a]
H1	7.50 ± 0.30	22.06 ± 1.96	2.40
H2	9.17 ± 0.31	27.73 ± 0.41	3.28
H3	12.53 ± 0.06	31.80 ± 0.30	4.12
H4	14.57 ± 0.25	34.80 ± 0.56	4.40
H5	18.63 ± 0.25	39.25 ± 1.32	5. 9
C1	14.60 ± 0.26	39.48 ± 1.41	6.10
C2	17.60 ± 0.30	45.65 ± 0.07	6.55
C3	19.20 ± 0.26	57.04 ± 1.07	7.12
C4	21.50 ± 0.36	62.91 ± 0.83	> 8
C5	25.43 ± 0.35	71.12 ± 0.29	> 8

Mean ± SD; [a] n = 6

Moisture absorption test

The moisture absorption studies give an indication of the relative moisture absorption capacities of polymers and whether the formulations maintain their integrity after moisture absorption. The order of increasing moisture absorption was HPMC K4M < carbopol 934 (Table 4). This may be due to the more hydrophilic nature of the polymer carbopol.

In vitro retention time

The *in vitro* retention time is one of the important physical parameter of buccal mucoadhesive tablet. Formulations H1 to H5 showed lower retention time when compared to the formulations C1 to C5. As the concentration of polymer increased, the retention time increased. This test reflects the adhesive capacity of polymers used in formulations. The results revealed that carbopol containing formulations showed better bioadhesion than the HPMC K4M.

Surface pH

Surface pH evaluation of oral mucosal dosage forms is an important characterization study. An acidic or alkaline pH may cause irritation to the oral mucosa. It was therefore necessary to determine if any extreme surface pH changes occurred with the tablets during the drug release period under investigation. The surface pH of the tablets remained fairly constant at a pH of approximately 6.5-7.0 over the 8 hrs test period, confirming that the surface pH of the tablets was within the neutral conditions of the saliva, pH 5.8-7.1 and that no extremes in pH occurred throughout the test period. These results suggested that the polymeric blend identified was suitable for oral application owing to the acceptable pH measurements.

In vitro drug permeation

Based on the *in vitro* drug release, *in vitro* residence time, moisture absorption and bioadhesion strengths of all formulations, the H3 formulation was selected for in vitro permeation studies. The oral mucosa of pigs resembles that of humans more closely than any other animal in terms of structure and composition and therefore porcine buccal mucosa was selected for drug permeation studies.

The results of drug permeation from buccal tablets through porcine buccal mucosa reveal that piroxicam was released from the formulation and permeated through porcine buccal membrane and could possibly permeate through the human buccal membrane. The drug permeation was slow and steady (Fig. 3) and 26.52 ± 0.19% of piroxicam permeated through the buccal membrane in 8 h with a flux of 0.038 mg h^{-1} cm^{-2}.

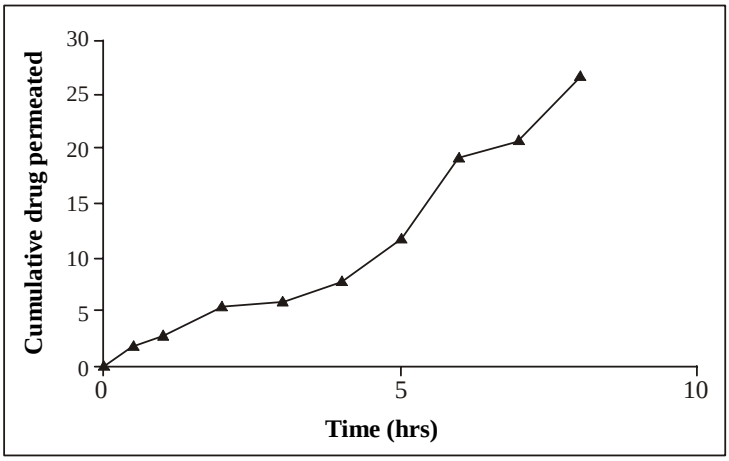

Fig. 3: *In vitro* permeation of piroxicam

Characterization of drug in buccal tablets

In IR spectrum of pure piroxicam (Fig. 4), the presence of peaks at 2979.48 cm^{-1} (OH stretching), 3381.30 cm^{-1} (NH stretching), 1634.17 cm^{-1} (C = O group) were characteristic to that of the pure drug, IR spectrum of physical mixture of piroxicam and HPMC K4M (Fig. 5), physical mixture of piroxicam and carbopol 934 (Fig. 6) and the IR spectrum of powder sample of tablet formulation H3 (Fig. 7). IR analysis revealed that there was no known chemical interaction of drug with polymers and other ingredients in prepared buccal tablets.

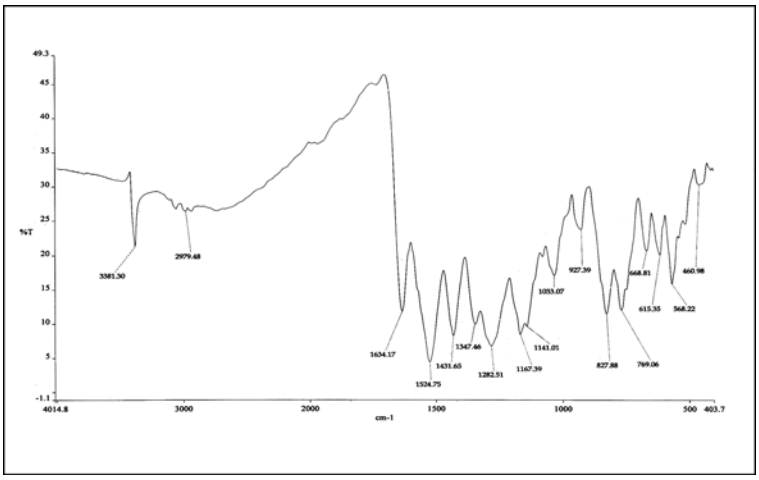

Fig. 4: IR spectrum pure piroxicam

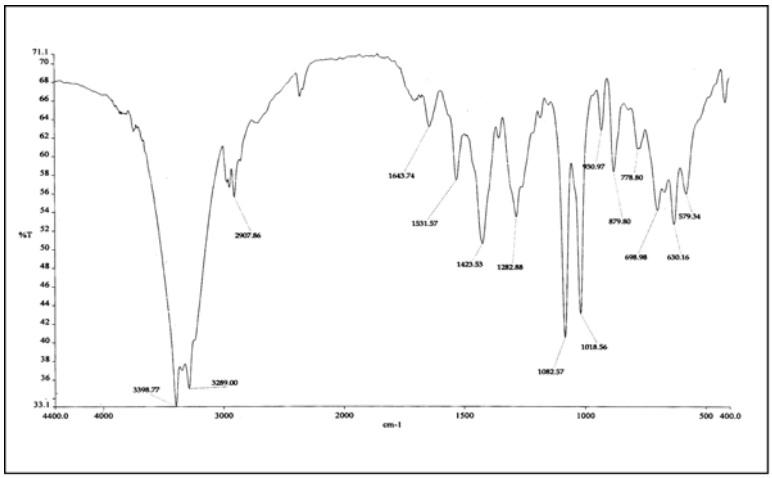

Fig. 5: IR spectrum physical mixture of piroxicam and HPMC K4M

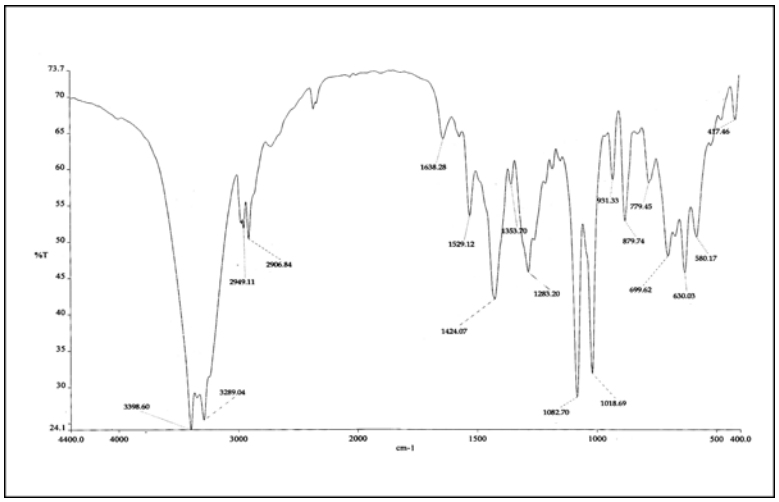

FIG. 6: IR spectrum physical mixture of piroxicam and carbopol 934

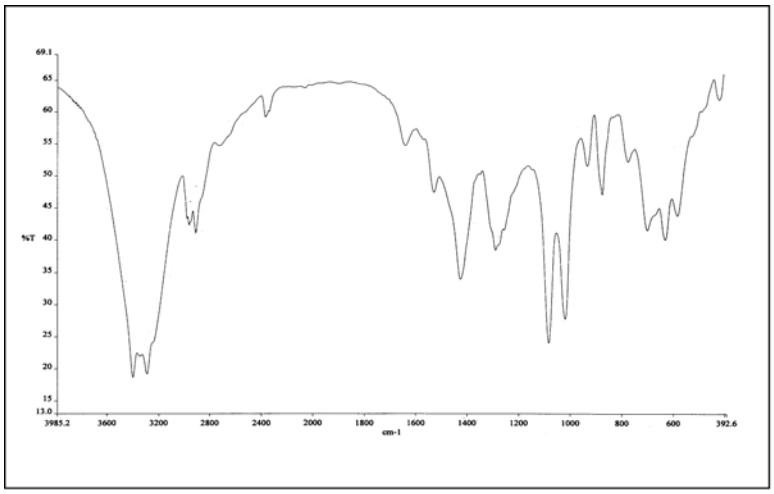

Fig. 7: IR spectrum of H3 formulation

DSC studies were performed to investigate the physical state of the drug in the tablets and drug interactions with polymers. Pure piroxicam (Fig. 8) showed a single sharp endothermic melting peak at 200ºC, which was unaltered in the thermogram of powdered sample of tablets evidencing the absence of interactions (Fig. 9). It reveals that the drug is in crystalline form without undergoing any degradation and that polymer (HPMC K4M) could be considered compatible with piroxicam.

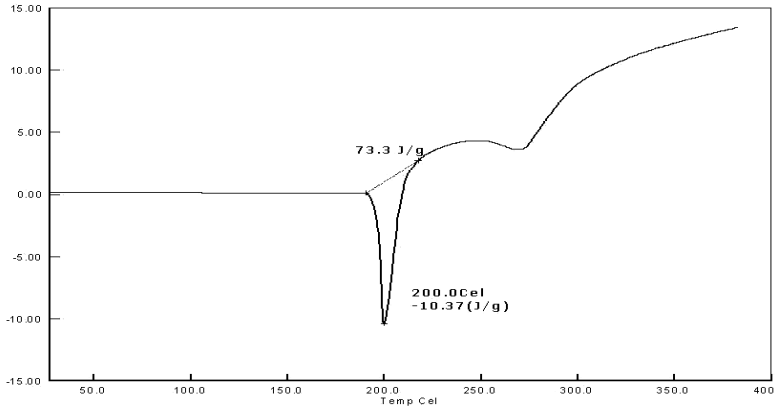

Fig. 8: DSC curves-pure piroxicam

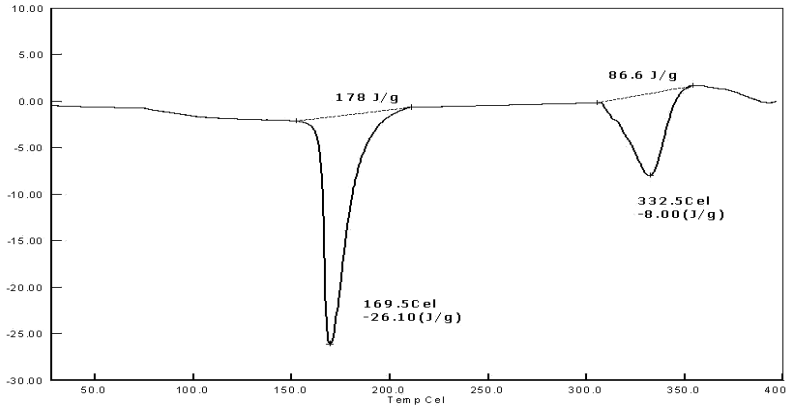

Fig. 9: DSC curves- H3 formulation

ACKNOLEDGEMENT

The authors wish to thank Daynamed Pharmaceuticals, Hyderabad and Zydus Cadila, Ahmedabad, specially Dr. P. Udupa, Principal in Manipal College of Pharmaceutical Sciences for providing the labfacility.

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Accepted : 16.10.2011