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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 were used in ratios of 1:0.25 to 1:1.5. The formulations were tested for *in-vitro* drug release, bioadhesive strength, moisture absorption, residence time and drug permeation through porcine buccal mucosa. Optimized 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 12.5gm of mucoadhesive strength, the FTIR results showed no evidence of interaction between the drug and polymers. The results indicated that suitable bioadhesive buccal tablets with desired permeability could be prepared. Stability of piroxicam buccal tablets was determined in natural human saliva; it was found that both piroxicam and buccal tablets were stable in human saliva.
Key words: Piroxicam ,Buccal tablets,formulation, evaluation.

Introduction

The oral cavity is an attractive site for the administration of drugs because of ease of administration.Various dosage forms like Tablets,Capsules, Liquid preparations are administered by oral route.In recent years delivery of therapeutic agents through buccal mucosa has gained significant attention.There is a possibility for mucosal (local effect)[1] and transmucosal (systemic effect)[2-3] drug administration.In first case the mucosal administration of drugs is to achieve site-specific release of drugs on the mucosa,where as ,in second case,transmucosal administration involves drug administration through mucosal barrier to reach the systemic circulation[4-6].Among the various transmucosal routes like nasal,rectal,vaginal ,ocular,pulmonary and buccal routes[7, 8], ,the buccal mucosa is an attractive alternative to the oral route of drug administration and it is a potential site for the delivery of drugs to the systemic circulation[9].

Therapeutic agents administered through buccal mucosa enters directly to the systemic circulation and there by circumvent 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, immobile mucosa, moderate permeability , less enzymatic activity and suitable for the administration of retentive dosage forms[10-12]. 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 therapeutic agent to patients who cannot be dosed orally to prevent accidental swallowing.[13]

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[14] and an ideal buccal adhesive system must have the following properties: should adhere to the site of attachment for few hours, should release the drug in controlled manner and should provide the drug release in an unidirectional way in to the mucosa[15].

Piroxicam is a non-steroidal anti-inflammatory (NSAID) drug and it is a non selective cyclooxygenase (COX) inhibitor used in the treatment of rheumatoid arthritis and osteoarthritis. It also possesses analgesic and antipyretic properties. Although the drug is well absorbed following oral administration, gastric irritation is still the most serious adverse effect associated with conventional route of drug administration[16-17].Thus need for an alternative drug delivery system, lead to the development of a new piroxicam formulation with better GI tolerability. Therefore, the aim of the present work was to develop a new bioadhesive sustain-release tablets for buccal delivery of piroxicam.

Materials and Method

Materials

Piroxicam was donated by Dynamed Pharmaceuticals, (Hyderabad, India). HPMC K 4M and Carbopol 934 were received as gift sample from Zydus Cadila, (Ahmedabad, India). Mannitol was purchased from Universal laboratories (Hyderabad, India). All other chemicals and reagents used were of analytical reagent grade and purchased from Himedia, (Hyderabad, India).

Bioadhesive tablets preparation

Piroxicam was mixed manually in polybags with different ratios of hydroxy propyl methylcellulose K4M (HPMC K4M) and carbopol 934 as mucoadhesive polymers and mannitol as diluent for 10 mins. The blend was lubricated with magnesium stearate for 3-5mins and then compressed into tablets by direct compression method using 8mm 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 were determined using a digital balance (Shimadzu, India) and thickness with digital vernier calipers (Mitutoyo, USA).

Assay of Piroxicam[18]

Twenty 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 (Elico, India) at 242nm. Each measurement was carried out in triplicate and the average drug content in the buccal tablet was calculated.

In-vitro release studies[19]

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 2x2 cm glass slide with a solution of cyanoacrylate adhesive. Then it was placed in the dissolution apparatus containing 500 ml of pH 7.4 phosphate buffer and paddle was rotated at 50 rpm at a temperature of 37 ± 0.5°C. Samples of 5 ml were collected at different time intervals up to 8hrs and analyzed spectrophotometrically. Experiments were performed for six tablets for each formulation and standard deviation was calculated.

Tissue Isolation[20]

Porcine buccal tissue was obtained from a freshly killed pig (slaughterhouse, Paloncha, India) weighing about 50 kg. After removal the tissue was stored in pH 6.6 phosphate buffer at 4°C and used within 3 hours. The epithelium was separated from the underlying connective tissue with a surgical technique making sure that the basal membrane was still present and the membrane was allowed to equilibrate for one hour in receptor buffer to regain lost elasticity. Slice thickness range from 2.1 to 2.5 mm.

Measurement o*f* Bioadhesion strength [15, 21]

Modified physical balance method was used for determining the *ex-vivo* bioadhesive strength. Fresh Porcine buccal mucosa obtained from a local slaughterhouse was stored in pH 6.6 phosphate buffer at 4^0C upon collection. The experiment was performed within 3 hours 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 gm was placed on the clamp for 5 mins 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 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.

Ex vivo residence time [22]

The *ex vivo* residence time is one of the important physical parameter of buccal mucoadhesive tablet. Each tablet side was wetted with 50µl simulated saliva and pressed over porcine buccal mucosa for 30

secs 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 37^0C. The paddle was adjusted at a distance of 5 cm from the tablet and rotated at 25 rpm (fig 2). The tablet behavior was observed until complete detachment.

Moisture absorption studies of buccal tablet [10]

Agar (5% w/v) was dissolved in hot water. It was transferred into petri dishes and allowed to solidify. Six buccal tablets (preweighed) from each formulation were placed in 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°C for one hour. Then the tablets were removed and weighed and the percentage of moisture absorption was calculated by using following formula:

% Moisture absorption = [(final weight – initial weight)/initial weight] x100.

Surface pH[23]

The buccal tablets were placed in glass tubes and allowed to swell in contact with pH 7.4 phosphate buffers (12ml). Thereafter, surface pH was measured by using pH paper placed on the surface of the swollen tablets. The mean of three readings was recorded.

***Ex vivo* permeation of buccal tablet [10, 22]**

The porcine buccal membrane was mounted between the donor and receptor compartment of 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 (37^0C) in the acceptor compartment was continuously stirred at 600rpm using a magnetic stirrer. The tablet was placed into the donor compartment and was wetted with 1ml 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 flux (J) through the membrane was calculated by using the equation 1.

$J = dQ / A\,dt$ …….. (1)

Where J is flux (mg $h^{-1}cm^{-2}$); dQ/dt is the slope obtained from the steady-state portion of the curve and A is the area of diffusion (cm^2).

Stability of buccal tablet [24, 25]

Stability study was performed in normal human saliva using the optimized formulation (H3), selection was based on the results of *in-vitro* drug release, moisture absorption, mucoadhesive strength and ex vivo residence time studies. The human saliva was collected (from human aged 24 years) and filtered. Each piroxicam tablet was immersed in petri dish containing 5ml of human saliva for 6 h and taken out at predetermined time interval. The piroxicam tablet was then observed for change in color, shape, collapse of the tablet and change in pH. The experiment was performed for 6 tablets.

Drug excipient compatibility study [26, 27]

In the present study FTIR and DSC were used as a tool to evaluate physical and chemical stability of prepared buccal tablets. 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 (company). The IR spectrum of pure piroxicam and pelletized powder of tablets were taken, interpreted and compared with each other. Thermo grams of pure piroxicam and powder sample of tablets were taken for DSC study. An empty aluminum pan was used as a reference. DSC measurements were performed at a heating rate of 5ºC/min from 50 to 400ºC using aluminium sealed pan. The sample size was 3.532 mg for pure drug and 5.477 mg for powder sample of tablets for measurements. During the measurement, the sample cell was purged with nitrogen gas.

Table 1: Composition of Piroxicam buccal tablets

Formulation	D : P	Drug	HPMC K4M	Carbopol 934	Mannitol	Mg stearate
H1	1:1	20mg	20mg	-	156mg	4mg
H2	1:2	20mg	40mg	-	136mg	4mg
H3	1:3	20mg	60mg	-	116mg	4mg
H4	1:4	20mg	80mg	-	96mg	4mg
H5	1:5	20mg	100mg	-	76mg	4mg
C1	1:0.25	20mg	-	5mg	171mg	4mg
C2	1:0.5	20mg	-	10mg	166mg	4mg
C3	1:0.75	20mg	-	15mg	161mg	4mg
C4	1:1	20mg	-	20mg	156mg	4mg
C5	1:1.5	20mg	-	25mg	151mg	4mg

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.

Table 3: Kinetic data of formulations

Formulation	Zero order (R^2)	First order (R^2)	Higuchi (R^2)	Peppas (R^2)	n	Hixson- crowel (R^2)
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

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

Formulation	Mucoadhesive strength (gm) [a]	% moisture absorbed [a]	*In-vitro* retention time (hrs)
H1	7.50 ± 0.30	22.06 ± 1.96	2 hours 40 mins
H2	9.17 ± 0.31	27.73 ± 0.41	3 hours 28 mins
H3	12.53 ± 0.06	31.80 ± 0.30	4 hours 12 mins
H4	14.57 ± 0.25	34.80 ± 0.56	4 hours 40 mins
H5	18.63 ± 0.25	39.25 ± 1.32	5 hours 9 mins
C1	14.60 ± 0.26	39.48 ± 1.41	6 hours 10 mins
C2	17.60 ± 0.30	45.65 ± 0.07	6 hours 55 mins
C3	19.20 ± 0.26	57.04 ± 1.07	7 hours 12 mins
C4	21.50 ± 0.36	62.91 ± 0.83	Above 8 hours
C5	25.43 ± 0.35	71.12 ± 0.29	Above 8 hours

Mean ± SD; [a] n = 6. (Statistical analysis, foot note)

Table 5: Stability data of buccal tablets in normal human saliva

Time (hrs)	Color change[+]	Thickness (mm)[a]	Change in shape Diameter (mm)[a]	Collapsing[+]
0	No	3.54 ± 0.01	8.01 ± 0.01	-
1	No	3.60 ± 0.01	8.17 ± 0.01	No
2	No	3.71 ± 0.01	8.31 ± 0.01	No
3	No	3.90 ± 0.01	8.54 ± 0.01	No
6	No	4.09 ± 0.01	8.70 ± 0.01	No

[+] Visual observation, Mean ± SD, [a] n= 6

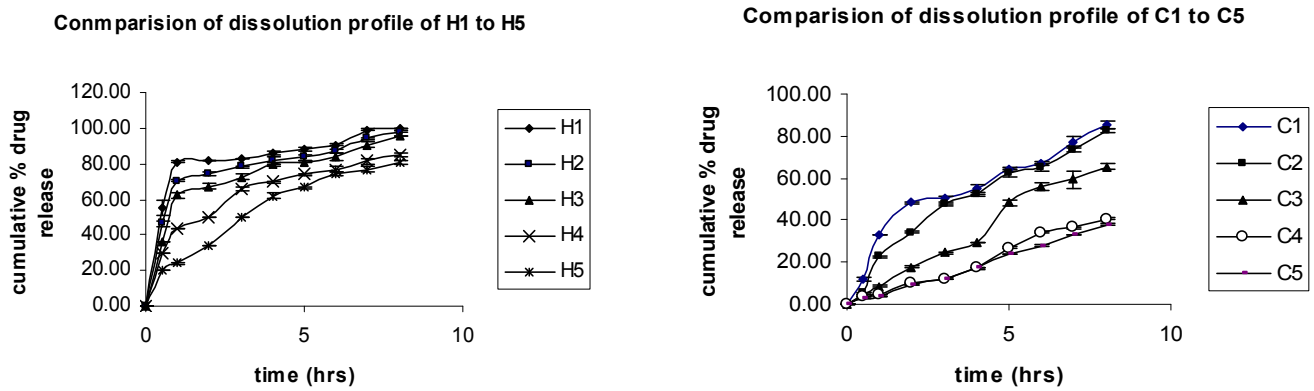

Fig 1: Drug release profile of Piroxicam buccal tablets formulated with a) HPMC K4M, b) Carbopol 934 (Mean ± SD, n = 3).

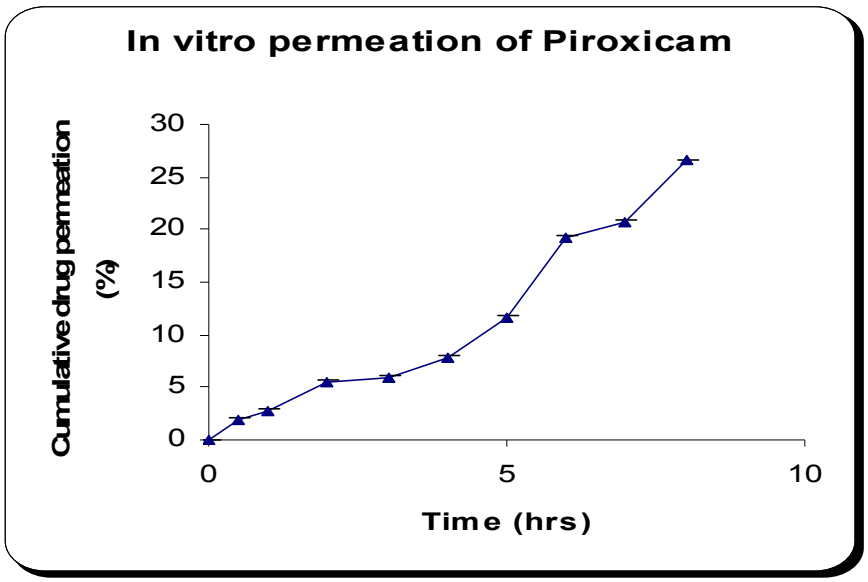

Fig 2: *In-vitro* permeation of piroxicam

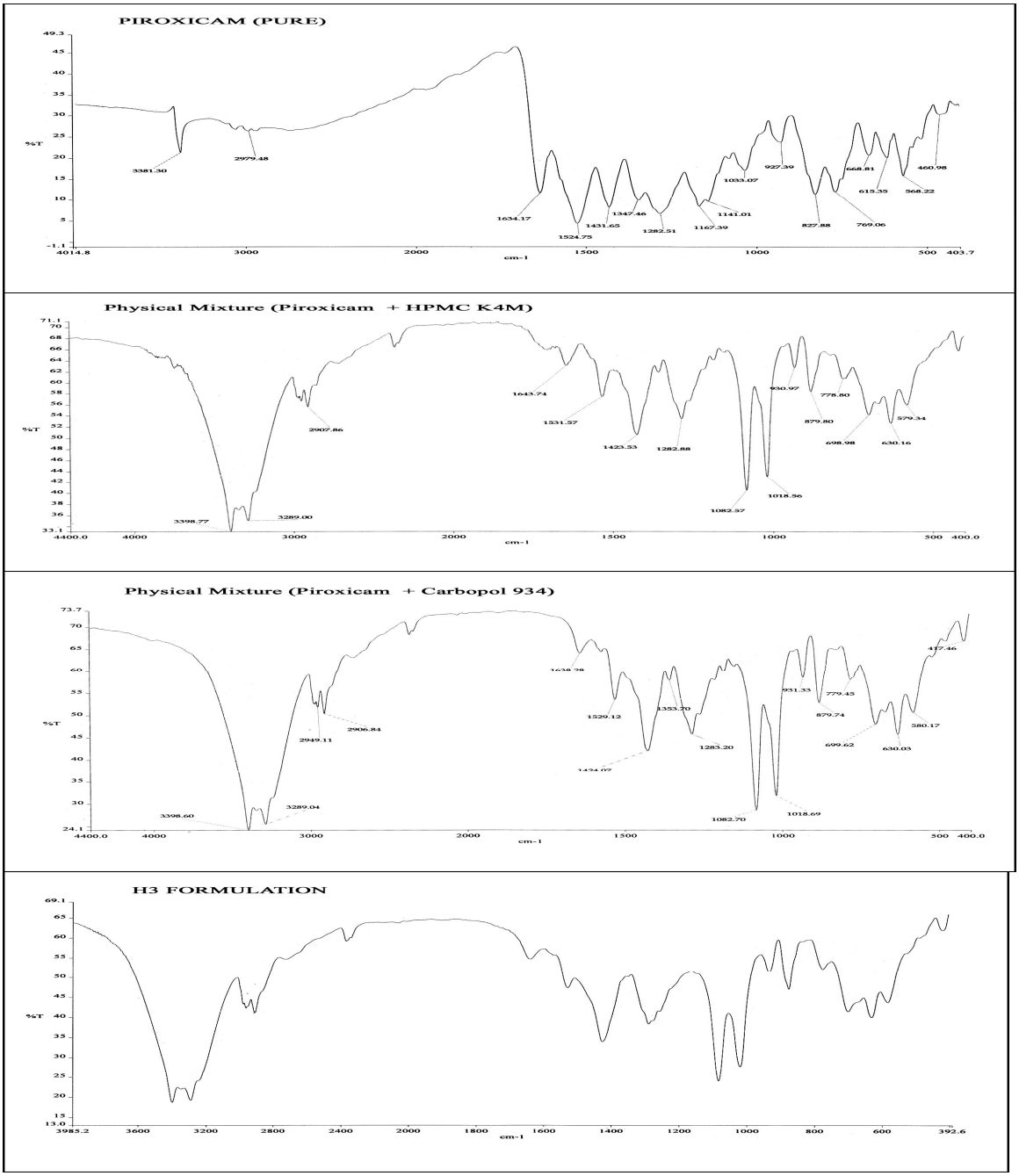

Fig 3: IR spectrum of a) pure piroxicam
b) physical mixture of piroxicam and HPMC K4M
c) physical mixture of piroxicam and carbopol 934 d) H3 formulation

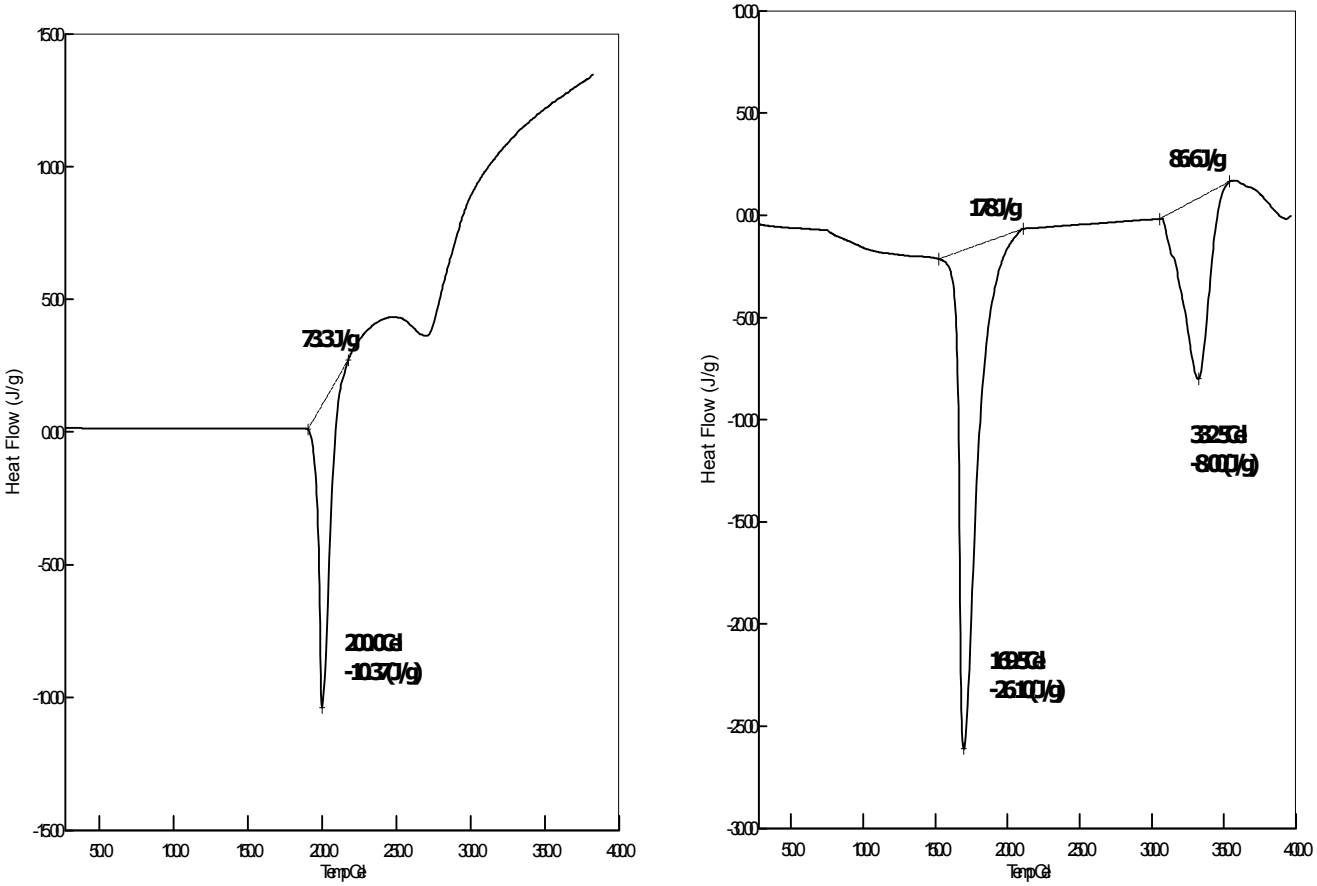

Fig 4: DSC curves of a) pure piroxicam and b) H3 formulation

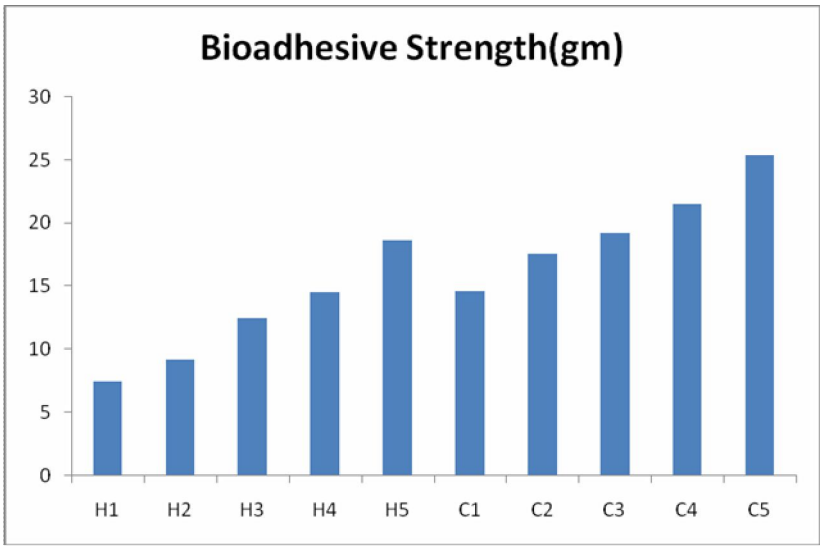

Fig 5: Bioadhesive strength of all the formulation

Results and Discussion

The weight variation and the thickness of all the formulations (Table 2) were within the acceptable 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 to 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 tablets were optimized on the basis of trail preparation of tablets. The hardness of all prepared tablet were in the range of 3.5 to 4 kg/cm^2.Hardness increased as the amount of concentration of the polymers increased.

Drug dissolution profile of various formulation prepared are shown in figures 1 and 2. Piroxicam was almost completely released from all the formulation in 8 hour study. The release of piroxicam from formulation varied according to the type and ratio of matrix forming polymers. Biphasic release was observed in formulation containing HPMC K4M polymer. It is apparent from the plot that the drug release could be governed by polymer content in the formulation. Release rates slowed down when the concentration of HPMC K4M or carbopol 934 increased from 1:1 to 1:5 ratios and 1:0.25 to 1:1.50 in H and C series 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 with longer diffusional path. In this study the results followed the above predictable behavior. Formulations containing lower concentration of either HPMC K4M or carbopol in H and C series respectively, tended to release the drug immediately in short period of time, while the release slow down as the concentration of the matrix forming polymer is increased, thus conforming the vital role of the matrix forming polymer in the drug release of piroxicam buccal tablets.

The release mechanism of piroxicam from buccal tablets was studied by using the following simple power equation 2

$$M_t/M\infty = K^n t^n \quad \text{.....(2)}$$

Where $M_t/M\infty$ is the fraction of drug released at time t.K represents a constant, incorporating structural and geometrical exponent and is characteristic of the buccal devices; n is the release constant describing the mechanism of drug release. For non fickian release, the value of n falls between o.5 to 1.0,while in case of fickian diffusion n 0.5,for zero order release (case II transport) n=1 and for super case II transport greater than 1. The values of n are estimated by linear regression of log ($M_t/M\infty$) versus log t [24] .The calculated parameters from this equation are given in table 3 and the values were found to be in the range of 0.5 to 1.0 for carbopol containing formulation, indicating the release of piroxicam to be non fickian. While HPMC K4 containing formulation showed fickian diffusion controlled mechanism except H5 formulation. In the kinetic study the order of piroxicam release for the optimized formulation were studied by plotting log percentage cumulative retained versus time curve and it followed first order kinetics.

The bioadhesion strength of all the formulations is given in Table 4 & fig 5. The bioadhesive strength was influenced by the type and ratios of bioadhesive polymers. In all the formulations, as the polymer concentration increased, the mucoadhesive strength increased. The higher bioadhesive strength of the carbopol may be due to the formation of secondary bonds with mucin and entanglement and interpenetration of polymeric chain with mucin. 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.

The moisture absorption study reveals an indication of the relative moisture absorption capacities of bioadhesive 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 bioadhesive polymer carbopol.

The *Ex vivo* residence time was determined by using specially designed apparatus. Formulations H1 to H5 showed lower residence time when compared to the formulations C1 to C5. As the concentration of mucoadhesive material 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.

The surface pH was determined in order to investigate the possibility of any side effects, in the oral cavity. An acidic or alkaline pH may cause irritation to the buccal mucosa. It is 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 formulation depends on the nature of polymer. Surface pH of the optimized formulation H3 was found to be 6.5-7 (near to neutral pH).It was suggesting that neutral pH of the formulation does not cause any irritation and biocompatible to buccal mucosa.

The stability studies are generally performed in phosphate buffer, whose pH is similar to buccal cavity. But, the stability studies performed in normal human saliva would be more accurate to mimic the stability of the piroxicam buccal tablet in oral cavity *in vivo*. Hence the stability of buccal tablet was examined in natural human saliva. Based on the results of *ex vivo* mucoadhesion, *in-vitro* release studies, moisture absorption, formulation H3 was selected as optimized formulation among the other formulations.

Therefore the stability studies were performed only on the optimized formulation (H3) and the results are shown in table 5. The piroxicam buccal tablet did not exhibit any change in color or shape, which reveals that the tablets having sufficient stability in the human saliva. Physical properties of the tablet such as thickness and diameter slightly changed due to swelling of the system in human saliva. But, buccal tablet did not collapse in human saliva until the end of the study, confirming that the device strength was sufficient.

Based on the *in-vitro* drug release, *ex vivo* residence time, moisture absorption and bioadhesion strengths of all formulations, the H3 formulation was selected for *ex vivo* 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 drug permeation from buccal tablets through porcine buccal mucosa revealed that piroxicam 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 2) and 26.52 ± 0.19% of piroxicam permeated through the porcine buccal membrane in 8 hrs with a flux of 0.038 mg $h^{-1}cm^{-2}$.

In IR spectrum of pure piroxicam, 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 pure drug and all of them remained unaltered in IR spectrum of powder sample of tablets (H3). IR analysis (fig 3) revealed that there was no known chemical interaction of drug with polymers and other ingredients in prepared tablets.

DSC studies were performed to investigate the physical state of the drug in tablets and drug interactions with polymers. Pure piroxicam showed a single sharp endothermic melting peak at 200ºC, which was unaltered in the thermogram of powdered sample of tablets (fig 4) evidencing the absence of interactions. It reveals that the drug is in crystalline form without undergoing any degradation and that polymer (HPMC K4M) could be considered compatible with piroxicam.

From the IR studies, important function group IR bands of drug, polymers and optimized formulation were identified. Characteristic IR bands of piroxicam includes the presence of peaks at 2979.48 cm^{-1} (OH stretching), 3381.30 cm^{-1} (NH stretching), 1634.17 cm^{-1} (C=O group) which remained unaltered in IR spectrum of powder sample of tablets (H3). IR analysis (fig 3) revealed that piroxicam and polymers were compatible in the formulation. DSC studies were performed to investigate the physical state of the drug in tablets and drug interactions with polymers. Pure piroxicam showed a single sharp endothermic melting peak at 200ºC, DSC thermogram of optimized formulation showed sharp distinct endothermic peak for piroxicam and which was correspond to individual drug and polymer without exhibiting any modification. This indicates that piroxicam and polymers are compatible in a prepared formulation. It also reveals that the drug is in crystalline form without undergoing any degradation.

Conclusion

Development of bioadhesive buccal drug delivery of piroxicam is one of the alternative routes of administration to avoid high gastric irritation and sustain release. In this present study H3 formulation comprises of piroxicam and HPMC K4M (1:3) showed optimum drug release and satisfactory bioadhesive properties. Thus the study revealed that the piroxicam buccal tablets showed good mucoadhesion time with sustained release of drug for more than 8 hours. The optimized formulation also showed satisfactory surface pH and physical parameters, effective *in vitro* permeation, satisfactory stability and comfortability in the oral cavity. From the results of present investigation it can be concluded that piroxicam can certainly be administered through the oral mucosa and HPMC K4M is suitable for development of buccoadhesive system. Further work is recommended to support its efficacy claims by pharmacodynamic and pharmacokinetic studies in human beings.

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