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FORMULATION AND EVALUATION OF MUCOADHESIVE BUCCAL PATCHES OF PIROXICAM

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ABSTRACT

The main objective of present investigation to formulate and evaluate mucoadhesive buccal patches of Piroxicam, using solvent casting method. HPMC K100 M were used as a mucocoadhesive polymer and PEG 400 used as a plasticizer as well as penetration enhancers. The formulated patches of piroxicam were evaluated for their appearance, weight variation, thickness, folding endurance, surface pH, swelling index, drug content, % elongation, mucoadhesive strength, in vitro drug release, kinetic release study and stability study. Among all formulated batches (S1-S8) of buccl patches batch S6 showing maximum drug release after 8 hours 94.77 % and mucoadhesive strength 10.21±0.35g). The stability study optimized batch S6 doesn't show any changes with respect to previous evaluation carried out before stability study. It may concluded the mucoadhesive buccal patches of Piroxicam were successfully prepared using HPMC K100 M by solvent casting method, evaluated & it is better alternative to conventional drug delivery for the management of pain and arthititis.

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INTRODUCTION

The oral route is the most preferred route for the administration of therapeutic agents because of its low cost, ease of administration and high level of patient compliance. However, many therapeutic drugs have been reported which undergoes extensive presystemic elimination by gastrointestinal degradation and or hepatic metabolism results in less systemic bioavailability, short duration of therapeutic action, and formation of inactive or highly toxic metabolites. The choice of another route of drug administration via parenteral, transdermal, mucosal route may avoid presystemic elimination or hepatic first-pass metabolism and the plasma level of drug can be maintained effectively or efficiently in the systemic circulation[1,2,3,4].

Transdermal route is unsuitable for maintaining drug plasma level in systemic circulation because of skin the main barrier. In the parentral administration drug directly enter into the systemic circulation and efficiently maintain plasma level of drug. However, parentral route is not prefer because of the pain during the parentral administration, can't reverse a toxic dose, may be expensive and specialized trained person is required for administration[5,6,7,8].

Therefore the Oral mucosal drug delivery system is widely applicable as novel site for administration of drug for immediate and controlled release action in various body cavities, like the nasal, buccal, ocular, rectal and vaginal mucosae has the benefit of bypassing the hepatic first-pass elimination associated with oral administration. Because of the dual biophysical and biochemical nature of these mucosal membranes drugs with hydrophilic and lipophillic nature can be rapidly absorbed[9,10.]

Piroxicam (PX) is one of the most effective non-steroidal, anti-inflammatory drug of the oxicam derivative which also having anti-pyretic activity in numerous types of pains such as used in the treatment of rheumatoid arthritis and osteoarthritis. Even though the drug is well absorbed through oral route, gastric irritation is still the most serious adverse effect. Thus there is a need for another drug delivery system with improved GI tolerability. Buccal administration of drugs provides a useful route of administration for both systemic and local actions and bypasses first-pass effects and avoids GI side effects[11,12].

MATERIALS AND METHODS

The pure piroxicam was obtained as a gift sample from Flamingo pharmaceutical Nanded. Hydroxy propyl methyl cellulose (HPMC K100 M) and polyethylene glycol 400 (PEG 400) were obtained from Research-Lab Fine Chem Industries, Mumbai.

PREPARATION OF MUCOADHESIVE BUCCAL PATCHES

The buccal patches of piroxicam were prepared by using solvent casting method. Weighed accurately amount of polymer dispersed in a beaker containing distilled water with stirring on magnetic stirrer. Add Poly ethylyne glycol (PEG)-400 to the polymeric solution during addition of plastisizer continuous stirring is necessary to prevent lump formation. Weigh accurately amount of Piroxicam and dissolve in distilled water which gives the suspension of piroxicam. Add the piroxicam suspension to the solution of polymer and plastisizer with continuous stirring. The solution was mixed continuously on the magnetic stirrer to get semisolid consistency. The resulting solution was casted on to glass ring kept on the surface of mercury in petri-plates and allowed to dry in oven. The dried films were cut into 2×2cm diameter pieces and kept in desiccator till further use.

Table no. 1: Formulation of Mucoadhesive Buccal patches.

Ingredients	Formulation Batch Codes (Quantity in mg)							
	S1	S2	S3	S4	S5	S6	S7	S8
Piroxicam	160	160	160	160	160	160	160	160
HPMC K100 M	125	150	175	200	225	250	275	300
PEG-400(ml)	02	02	02	02	02	02	02	02
Distilled water (ml)	15	15	15	15	15	15	15	15

EVALUATION OF FORMULATED BUCCAL PATCHES

Compatibility of Piroxicam with excipients

FT-IR

FT-IR spectra for pure Piroxicam and Different polymers acquired at room temperature using FT-IR spectrophotometer (FTIR-8400S, Shimadzu, Japan) in transmittance mode. The samples were ground in a mortar, mixed with Nujol and placed between two plates of KBr and compressed to form a thin film. The sandwiched plates were placed in the infrared spectrometer and the spectra were obtained. Scanning was performed between wave numbers 4000-400 cm-1.

Differential scanning colorimetry analysis

Method for estimating the physical interaction between drug and polymers used for the formulation of different dosage form is thermal analysis by DSC.

Appearance

The formulated buccal patches visually observed for their color and transparency [13,14].

Surface texture

By simply touching the surface of the formulated buccal patch the surface texture can be evaluated[15,16].

Thickness of the patch

The thickness of prepared buccal patch of piroxicam was measured at five different points of the each patch by Vernier Caliper. The average thickness was calculated from the five points[16,17].

Weight variation

The average weight of 5 patches of each formulated batch was determined by weighing individually on a Digital Balance[18,19].

Folding endurance

The Folding endurance is a mechanical measure used to find out strength and elasticity of patches. The folding endurance was determined manually for the prepared buccal patch by repeatedly folding the patch at the same place until it broke. The number of times the patch could be folded at the same place without breaking or cracking gave the value of folding endurance[20,21].

Surface pH

The buccal patches was allowed to swell on the surface of agar plate (the agar plate is prepared by dissolving agar 2% w / v in warmed phosphate buffer pH 6.8 under stirring then poured to Petridish to solidify at room temperature) for two hour at room temperature and pH was noted down by bringing electrode in contact the surface the pH, allowing it equilibrate for 1 minute[22,23].

Swelling index

The weight of the buccal patch was measured by digital electronic weighing balance. Patches are placed on the surface of an agar plate and allowed to swell by keeping it an incubator at 37 ºC and the diameter is measured at predetermined time intervals for 90 minutes. Swelling index was calculated from following equation[24,25].

$$\text{Swelling index} = (W2 - W1 / W1) \times 100$$

Where
SI (%) is percent swelling.
W2 is the swollen patch weight.
W1 is the initial weight of the patch.

Drug content estimation

Drug content uniformity was determined by dissolving the patch in 100 ml of phosphate buffer (pH 6.8) for 4 h under occasional shaking. The 1 ml solution was remove and diluted with isotonic phosphate buffer pH 6.8 up to 10 ml, and the resultant solution was filtered through a whatman filter paper. The drug content was then determined after appropriate dilution at 242 nm using a UV spectrophotometer (Shimadzu, 1800, Japan)[26,27].

Muco-adhesive strength

Muco-adhesive strength of the patch was measured on a modified physical balance. The fresh goat buccal mucosa was collected from a local slaughterhouse and used within 2 h of slaughter. Cut in to a piece of 3 cm and washed with phosphate buffer pH 6.8. A piece of buccal mucosa was stick on the inverted 50ml beaker which is place in the center of 250ml beaker conataing phosphate buffer (pH 6.8). The patch was stuck to the lower side of glass vial with cyanoacrylate adhesive. Two pans of the balance were balanced with 5 gm weight on the right hand side pan. A weight of 5 gm was removed from the right hand side pan, which lowered the pan along with the patch over the mucosa. The balance was kept in this position for 5 min. contact time. The water was added slowly by hand (100 drops/min.) to the right-hand side pan until the patch detached from the mucosal surface. The weight in grams required to detach the patch from the mucosal surfaces gave the measure of muco-adhesive strength. The weight, in gramms, needed to detach the patch from the mucosal surface (goat buccal mucosa) results the measure of muco-adhesive strength[27,28].

Percent Elongation Break

The elongation at break is a determination of the maximum deformation the film can undergo before tearing apart. It is calculated using the following equation[29].

$$\%\text{Elongation at break} = L_2\text{-}L_1/L_1 \times 100$$

Where
L_2Increase in length of break
L_1Initial film length

I*n Vitro* drug release study

The *in vitro* drug release study of piroxicam buccal patch through the cellophone membrane was performed using a Franz diffusion cell at 37.0±0.5°C. the cellophone membrane was mounted between the donor and receptor compartments. The patch was placed on the cellophone membrane, and the compartments were clamped together. The donor compartment was filled with 1 ml of phosphate buffer (pH 6.8). The receptor compartment was filled with 200 ml phosphate buffer (pH 6.8), and the hydrodynamics in the receptor compartment were maintained by stirring with a magnetic beed at 50 rpm. At predetermined time intervals, 1 ml sample was withdrawn and replaced with fresh medium and absorbance of the samples were measured at 242nm, and the cumulative percentage release was calculated. The experiments were performed for each formulated batch[30,31].

Drug release kinetic study

The rate and mechanism of release of Piroxicam from formulated muco-adhesive buccal patches were analyzed by fitting the dissolution data into following exponential equations[29,30,31,32].

Zero order release equation:

$$Q = K0t \quad \text{(1)}$$

Where Q is the amount of drug released at time t and K0 is the zero order release rate constant.

The first order equation:

$$\log (100 - Q) = \log 100 - K1t \quad \text{(2)}$$

Where, K1 is the first order release rate constant.

The Higuchi's equation:

The drug release data was fitted to the Higuchi's equation

$$Q = K2t1/2 \quad \text{(3)}$$

Where, K2 is the diffusion rate constant.

The Korsmeyer-Peppas equation/

The drug release data was also fitted to the Korsmeyer-Peppas equation, which is often used to describe the drug release behavior from polymeric systems:

$$\text{Log } (Mt/M^{\infty}) = \log K + n \log t \quad \text{(4)}$$

Where,

Mt is the amount of drug released at time t,

M∞ is the amount of drug release after infinite time,

K is a release rate constant and n is the diffusion exponent indicative of the mechanism of drug release.

The diffusion exponent was based on Korsmeyer-Peppas equation.

Hixson-Crowell recognized that area of the particle is proportional to the cubic root of its volume, and derived an equation as follows.

$$W_0^{1/3} - W_t^{1/3} = Kst \quad \text{(5)}$$

Where, Wo is the initial amount of drug, Wt is the remaining amount of drug in dosage form at time t, KS is a constant incorporating the surface volume relation. The graphs are plotted as cube root of percent drug remaining versus time

Stability study

Formulation batch S6 has shown best results amongst all 8 batches. So stability study was carried out on formulation batch S6. Different patches were kept in on 40 ^{0}C with 75% respectively for the period of three months and evaluated after three months[32,33].

RESULT AND DISCUSSION

Compatibility of Piroxicam with excipients

FTIR shows that all above characteristic peaks of Piroxicam observed near about their respective values so it has been decided that there is no incompatibility between polymers and pure drug.

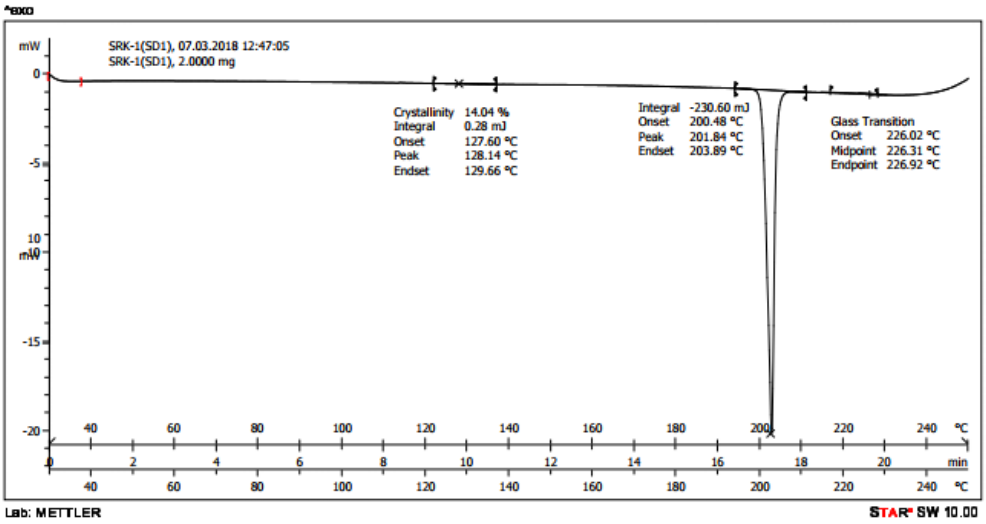

Figure No. 1: DSC of Pure Drug Piroxicam.

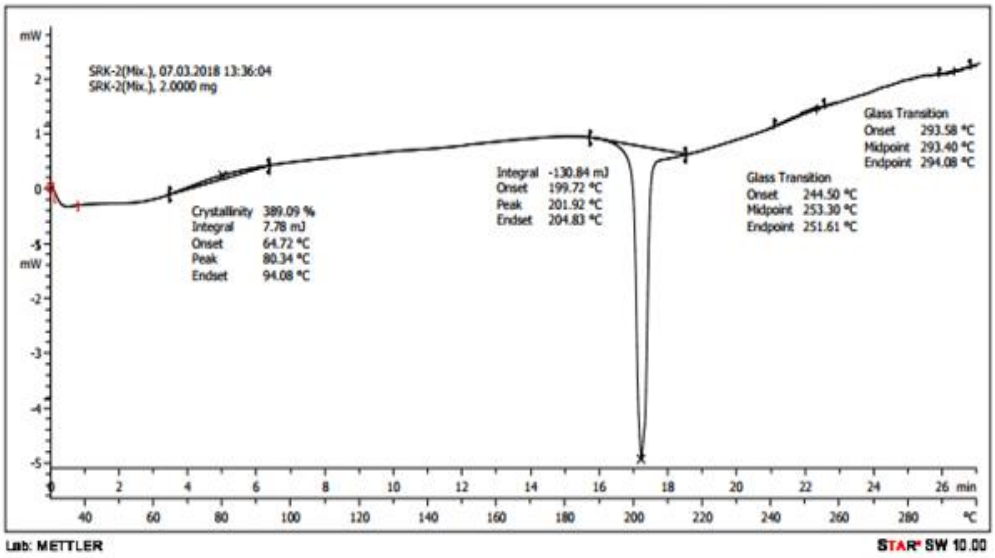

Figure no. 2: DSC of piroxicam with HPMC K100M.

The DSC study was performed to identify the physical state of drug in the mucoadhesive buccal patches and drug interactions with polymer. Pure Piroxicam showed a single sharp endothermic melting peak at 201.^{0C}, which was unchanged in the thermogram of powder of buccal patches which evidence of the absence of interactions showed in.it reveals that the drug is in crystalline form without undergoing any degradation and that polymer HPMC K 100M could be compatible with Piroxicam.

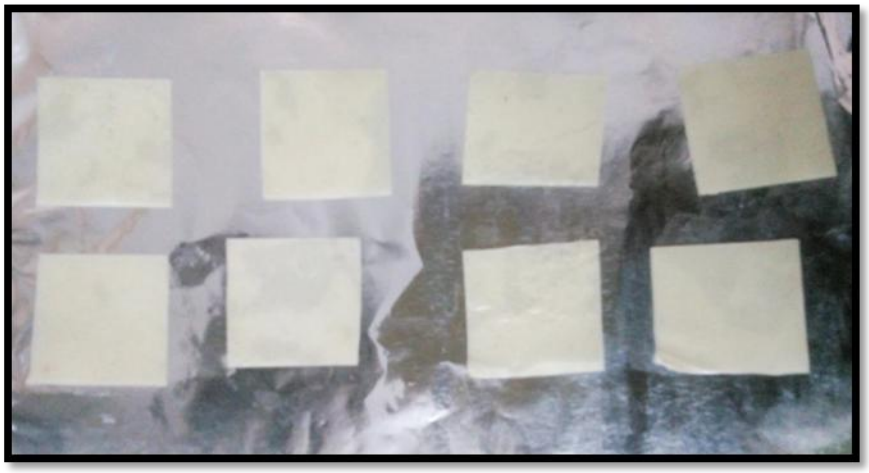

Figure no. 3: Formulated Buccal Patches of Piroxicam.

Table no. 2: Thickness, weight variation, folding endurance and surface pH of patches.

Batch Code	Thickness (mm±SD)	Weight Variation (mg±SD)	Folding Endurance (times)	Surface pH
S1	0.34±0.05	37.86±0.15	204±1.00	6.68±0.13
S2	0.40±0.10	40.79±0.18	202±2.82	6.56±0.11
S3	0.42±0.08	44.20±0.32	200±1.22	6.46±0.05
S4	0.48±0.08	47.30±0.40	198±1.58	6.48±0.16
S5	0.50±0.07	50.40±0.42	198±1.22	6.30±0.20
S6	0.52±0.04	53.40±0.35	195±2.54	6.32±0.08
S7	0.56±0.05	56.48±0.36	190±5.70	6.44±0.13
S8	0.60±0.07	59.75±0.20	187±3.16	6.74±0.15

Physical properties

The thickness of prepared buccal patch of piroxicam was found in the range of 0.34±0.05 mm to 0.60±0.07 mm. The weight of formulated buccal patches ranges in between 37.86±0.15 mg to 59.75±0.20 mg. The folding endurance of the patches was measured manually and the patches folded between 187±3.16 to 204±1.00 times.

The surface pH of formulated batches were found to be in the range of 6.68±0.13 to 6.74±0.15 for all formulations were almost within the range of salivary pH i.e. 6.0 to 7.4. Swelling index of batches like (S6, S7, and S8) found 26.29%, 26.85% and 26.33%, The percent elongation at break of all 8 formulated batches (S1-S8) were found in the range of 15% to 60%.

Swelling Index

The percentage swelling index taken at predetermined time intervals of 15minutes to 90 minutes for trial batches and 15 minutes for 120 minutes for final batches. The calculated percentage swelling

Table No. 3: Swelling Index of formulated batches.

Time (min)	Percentage of Swelling (%)							
	S1	**S2**	**S3**	**S4**	**S5**	**S6**	**S7**	**S8**
00	00	00	00	00	00	00	00	00
15	01.92	02.50	03.61	03.86	04.33	04.73	03.80	03.88
30	02.77	04.14	06.56	10.86	11.28	08.93	08.55	08.08
45	03.93	07.91	10.63	12.89	14.12	14.79	15.08	15.08
60	05.36	10.83	13.37	16.93	15.46	16.31	17.01	16.94
75	06.12	12.77	15.00	18.85	18.02	19.60	20.20	20.59
90	11.88	14.46	15.18	20.46	19.44	20.00	21.12	21.93
105	13.28	15.10	15.61	22.24	22.40	23.35	23.51	23.97
120	13.99	15.29	19.11	24.08	25.79	26.29	26.85	26.33

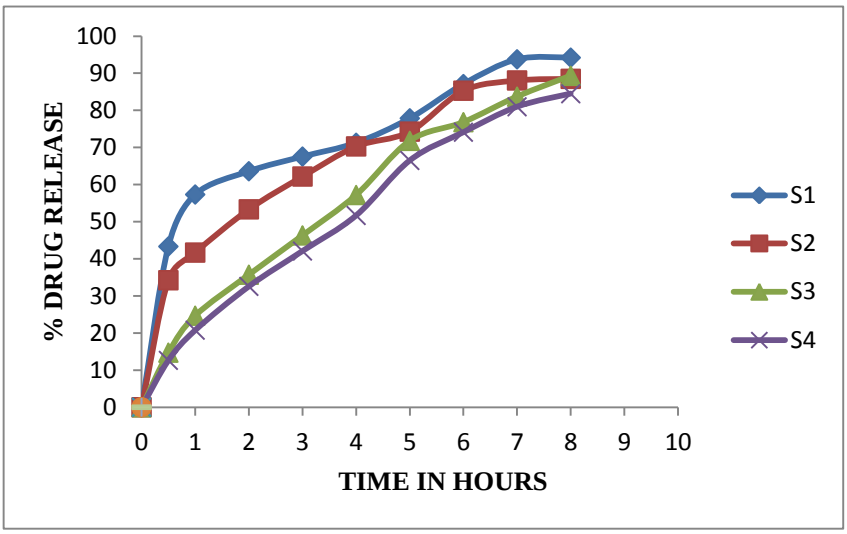

Figure No. 4: % Swelling Index S1-S8 Formulated Batches.

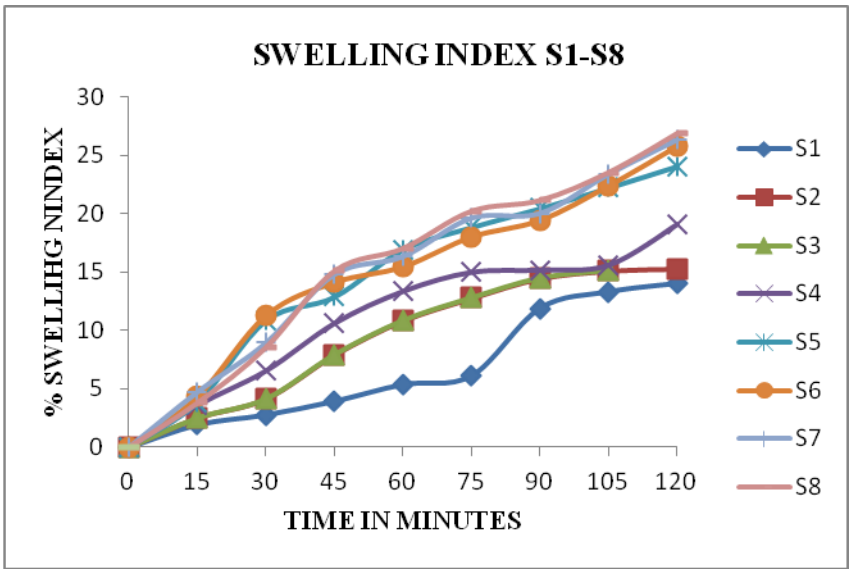

Figure No. 5: % drug release of formulated batches S1-S4.

Table No. 4: Drug content, Mucoadhesive strength, Force of adhesion, Elongation at Break of Formulated Buccal Patches.

Batch Code	Drug content (%)	Mucoadhesive strength (gms)	Force of adhesion (N)	Elongation at break (%)
S1	96.24	04.30±0.30	0.04	20
S2	90.30	05.75±0.32	0.05	25
S3	92.40	06.46±0.41	0.06	30
S4	88.90	08.09±0.85	0.07	30
S5	86.50	09.22±0.28	0.09	40
S6	95.60	10.21±0.35	0.10	45
S7	87.10	11.05±0.48	0.10	50
S8	93.40	13.22±0.71	0.12	60

Drug content

To evaluate the potential for efficacy the amount of drug in the buccal patches it is necessary to be determine drug content. The drug content in the buccal patches ranged from 86.50% to 96.24%, indicating the favorable drug loading and patches uniformity with respect to drug content.

The percent elongation at break

The percent elongation at break of all 8 formulated batches (S1-S8) were found in the range of 15% to 60%. The elongation at break values increase with the increase in polymer content.

Muco-adhesive strengths

The muco-adhesive strengths of all batches were found to be in the range of 04.30±0.30 gm to 13.22±0.71 gm respectively. As a result shows that an increasing in muco-adhesive polymers concentration increases the viscosity of the buccal patches hence increases muco-adhesive strength of patches.

In-*vitro* drug release

The *in-vitro* drug release of all batches was studied in phosphate buffer pH 6.8 by using Franz diffusion cell. The percentage drug release was found to be in the range of 75.80% to 94.77% respectively. The results show that increase in concentration of muco-adhesive polymers increase the viscosity of formulation hence decrease the drug release from the buccal patches and gives the sustain release of drug.

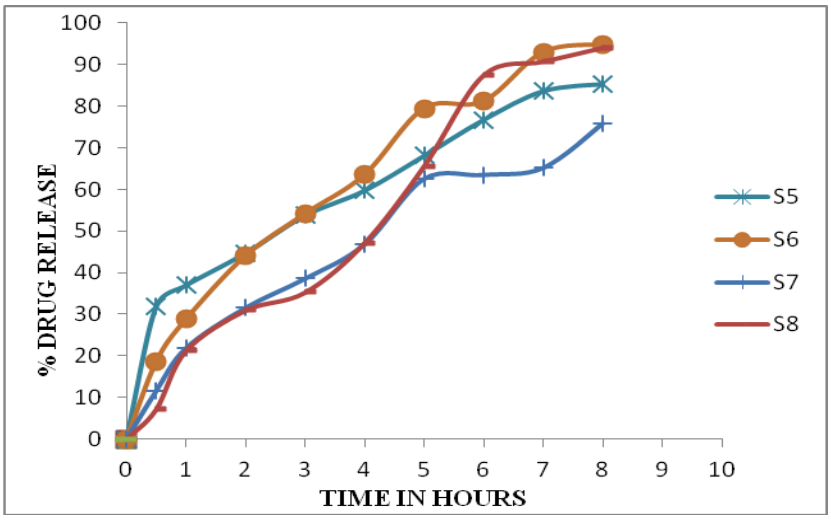

Figure No. 6: % drug release of formulated batches S5-S8.

Table No. 5: Release kinetic of Optimized Batch S6.

Formulation code	Higuchi	Zero Order	First Order	Hixoncrowell	Korsemeyer-Peppas	
	r^2	r^2	r^2	r^2	r^2	N
S6	0.98	0.97	0.89	0.67	0.99	0.59

Kinetics of drug release

The mechanism and Kinetics of drug release from batch S6 formulation was evaluated based on the Higuchi equation, Zero order, First order, Hixoncrowell equation and Peppas model. Correlation coefficient (r^2) and slope value for each equation in the range of (r^2=0.67 to 0.99 and n=0.59) was calculated. The diffusion exponent 'n' values of Korsemeyer-Peppas model was found to be in the range of 0.59 for the mucoadhesive buccal patches prepared by using HPMC K100 M as mucoadhesive polymer and PEG 400 as platisizer and as penetration enhancer. The study was shows that the buccal patches of piroxicam follows the korsmeyer peppas release order kinetic.

Stability study

Table No. 6: Stability Study of optimized batch.

Temperature	Time in months	Mucoadhesi ve strength (gm)	Swelling Index (%)	Surface pH Mean ± SD	% Drug Release
40^0C± 2^0C 75% RH	3	6.40	26.27	6.31	87.47

The stability study was performed according to ICH guidelines. The mucoadhesive buccal patches show very minor or little changes on physical appearance, like swelling index, surface pH, and muco-adhesive strength during the study period. The percentage drug release of mucoadhesive buccal patches kept in stability conditions were found to be 87.47% respectively after the end of 3 months.

CONCLUSION

On the basis of mucoadhesive strength (10.21±0.35g) and in vitro drug release (94.77% in 8h) from the formulated batches of buccal patches, batch S6 was concluded as optimized batch. The surface pH values were found in the range of 6.10±0.15 to 6.74±0.15 for all formulations were almost within the range of salivary pH i.e. 6.0 to 7.4. on the basis of above all evaluation It may concluded the mucoadhesive buccal patches of piroxicam were successfully prepared using HPMC K100 M by solvent casting method, evaluated & it is better alternative to conventional drug delivery for the management of pain and Arthititis.

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