Formulation and Development of Novel Proniosomal Formulation

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Abstract: - Nanotechnology is now frequently used to develop novel dosage formulations. The use of vesicular drug delivery systems is developing as a cutting-edge nanotechnology. Over traditional dosage forms, the delivery of medications employing colloidal particle carriers and liquid crystalline compact niosomal hybrids like niosome and proniosomes has peculiar advantages. The buccal film is a drug delivery method that has quickly become popular because it offers greater safety and efficacy of the drug molecule as well as a quicker onset of action. The proniosomes are formulated using nonionic surfactant which increases the solubility and bioavailability of the poorly soluble drugs especially for BCS Class II drugs. Because buccal mucosa is more accessible and less mobile than sublingual mucosa, it is more suited for retentive systems utilized for oral-mucosal drug delivery. Regarding mucosal (local effect) and transmucosal (systemic effect) medication. To get the medicine into the systemic circulation, it entails passing past the mucosal barrier. Because the medication content in buccal formulations may be significantly smaller than that in tablets and capsules, there may be a significant reduction in toxicity or unfavorable side effects. The buccal mucosa is more ideal for the insertion of a control release system since it is relatively porous, has a high blood supply, and is robust in comparison to other mucosal tissue. The buccal film is appropriate for the drugs which experience first pass metabolism and GI degradation. It limits the side effects and thus make it cost effective and a stable formulation

Keywords: - Proniosomes, Vesicular drug delivery, Buccal Drug delivery, Novel formulation, Bioavailability.

I. INTRODUCTION

The present research work aim is Formulation and Evaluation of Piroxicam Mucoadhesive Buccal Film by Solvent Casting Technique for Treatment of Dental Pain. By creating a mucoadhesive buccal film of the medicine and incorporating through the buccal delivery system, the issue of limited bioavailability and substantial first-pass metabolism can be resolved. The first pass effect and the hostile gastrointestinal environment are both avoided by the direct absorption of medicines into the portal vein. One of the main benefits of buccal drug delivery over peroral drug delivery is this. Currently, proniosomes are employed to improve drug delivery in addition to traditional niosomes. There are several reasons why the buccal mucosa might be a desirable location for the administration of therapeutic drugs into the bloodstream. It is possible to escape the first pass metabolism in the liver and intestine thanks to the direct drainage of blood from the buccal epithelium into the internal jugular vein. When given orally, several substances have poor bioavailability due in large part to this first-pass impact. Furthermore, because the mucosa lining the mouth cavity is easily accessible, a dose form can be placed to the necessary site and removed without difficulty in an emergency. The extremely effective NSAID piroxicam is chosen for treating rheumatoid arthritis, osteoarthritis, and other inflammatory disorders. Piroxicam side effects include ulcerative colitis, GI irritation, and peptic ulcers when used orally, however parenteral injections of the drug are more likely to cause significant pain and inflammation. Piroxicam's (a BCS class II medication) poor solubility is another significant issue. It takes about 2 hours after oral administration for it to start working therapeutically. In these situations, improved bioavailability with a quick beginning of action is crucial for this family of medications (analgesics). Because of this, some medications' oral delivery becomes a limiting factor. Drug-loaded buccal patches are a substitute that patients find to be a highly acceptable method of drug administration. It provides longer contact hours and more medication delivery system flux, improving

patient compliance. The oral mucosa receives additional systemic perfusion that is comparably higher than that of other mucosal layers, which has the extra benefit of promoting fast drug absorption. A possible alternative to existing modes of administration is the oral route of administration in the form of a "buccal patch."

II. MATERIALS AND METHOD

Materials

Piroxicam was procured from Sovereign Pharma PVT.LTD as a gift sample. Excipients such as Methocel of different grade were procured from Colorcon Asia Pvt Ltd as a gift sample. PEG, Methanol, Ethanol, were from Pallav chemicals Mumbai. All other chemicals and reagents used were of analytical grade.

Methods

Preformulation studies were carried out of the pure drug and excipients.

Preparation of the buccal film is done in two phases. The first is formulation of proniosomes using coacervation phase separation method. The other is loading this proniosomal formulation into the buccal film formed by solvent casting technique.

1. Preformulation Studies

a. Melting Point of the drug: - The melting point of Piroxicam drug was carried out using Capillary tube method.

b. FTIR Studies: - FTIR investigations verified Piroxicam's compatibility with excipients. Utilizing the potassium bromide disc (pellet) technique, an FTIR investigation was carried out. FTIR (IR Affinity S1, Shimadzu, Kyoto, Japan) was used to record the FTIR spectrum of the medicine Piroxicam in its purest form as well as a physical mixture of Piroxicam and other excipients.

c. Determination of the absorption maximum (λ max) of the drug: - Stock solution of the drug was prepared using PBS pH 7.4 with a concentration of 1000ppm. 1 ml was withdrawn from the stock solution and was diluted up to 10ml to give concentration of 100ppm, again diluted to give a concentration of 10ppm solution. Wavelength was scan from 200 to 400nm to determine the absorption maxima of the drug.

2. Method of Preparation

a. Formulation of Proniosomal Suspension

Proniosomes were formulated using the coacervation phase separation method, with some advancements using different surfactants from Span and Tween. The composition of different proniosomal formulations is outlined in table 1. In a glass vial, 10 mg of Piroxicam was added along with the surfactant and cholesterol. Add the required quantity of ethanol and heat it over a water bath at about 60-70 °C for 5 min by closing the glass tube to prevent loss of solvent while shaking until the complete dissolution of cholesterol. After complete dissolution of the solution, add 1 ml of phosphate buffer saline and warm for another 5 min until the formation of a clear or translucent solution. The formulation was cooled down at room temperature to get a clear milky white solution of proniosomes

Formulation Ingredients	Formulation Code					
	F1	F2	F3	F4	F5	F6
Piroxicam	52mg	52mg	52mg	52mg	52mg	52mg
Cholesterol	-	30mg	25mg	35mg	-	40mg
Soya Lecithin	30mg	-	25mg	-	35mg	-
Span 40	200mg	-	-	-	250mg	-
Span 60	-	-	250mg	-	-	-
Tween 20	-	300mg	-	-	-	-
Tween 60	-	-	-	350mg	-	400mg
Ethanol	1ml	1ml	1ml	1ml	1ml	1ml
PBS (pH 7.4)	2ml	2ml	2ml	2ml	2ml	2ml

Table no 1: - Composition of Proniosomal Suspension

b. Formulation of Mucoadhesive Buccal Film

The mucoadhesive buccal film is made using the solvent casting technique, which is one of the more straightforward approaches compared to other buccal film formulation techniques and the most extensively used manufacturing method for making films. The clarity and thickness homogeneity of the solvent casting process are superior to those of the extrusion method. This approach involves dissolving the necessary amount of polymer in distilled water. On the other hand, various excipients, and active pharmaceutical ingredients (API) are dissolved in an appropriate solvent system. The two solutions are then stirred together to create a homogenous mixture. "Casting solution" is the name given to the resulting solution. The resultant proniosomal suspension was loaded into the above homogenous mixture and then

was poured into the petri dish and was kept overnight for drying.

Formulation Code	Formulation Ingredients					
	Methocel E15	Methocel E4	Methocel Pure	PEG 400	Ethanol	Distilled Water
SBF1	1000mg	-	-	2ml	1ml	q. s
SBF2	-	1000mg	-	2ml	1ml	q. s
SBF3	-	-	1000mg	2ml	1ml	q. s
SBF4	500mg	-	-	2ml	1ml	q. s
SBF5	-	500mg	-	2ml	1ml	q. s
SBF6	-	-	500mg	2ml	1ml	q. s

Table no 2: - Composition of the placebo Mucoadhesive buccal film

The Optimized proniosomal suspension was loaded into the placebo buccal film.

III. RESULTS AND DISCUSSION

A. Preformulation Studies

a. *Melting Point of the drug*: - The melting point of Piroxicam drug was carried out using Capillary tube method. The melting point was found to be 199 to 200°C as shown in the figure no 1 and it complies with the Indian pharmacopoeia standard (IP), thus determines the purity of sample.

Figure No 1

b. *FTIR Studies*: Piroxicam powder's Fourier Transform Infrared Radiation (FT-IR) spectrum is depicted in Figure 2 below. The results show that the reference powder and the tested powder have the same spectra. By taking FT-IR spectra of the samples, it was possible to characterize the structural makeup of cholesterol. The existence of Piroxicam and cholesterol bands can be seen in the comparison of the spectra of pure Piroxicam powder with cholesterol. There were no incompatibilities and no additional bands appeared, as depicted in Figure 3. The mixture of Piroxicam and span 60 produces spectra like those in figures 4. The mixture of Piroxicam and HPMC K4M produces spectra like those in figures 5. There was no drug interaction, and no new bands debuted. The physical mixture of the drug Piroxicam with excipients was measured for its Infrared Radiation (IR) spectrum, and it was discovered to be consistent with the reported peaks. Though there may not have been any conceivable interactions between the medicine and excipients, no significant peak shifts or production was found. It was discovered that the FTIR spectrum was pure, stable, and unchanged.

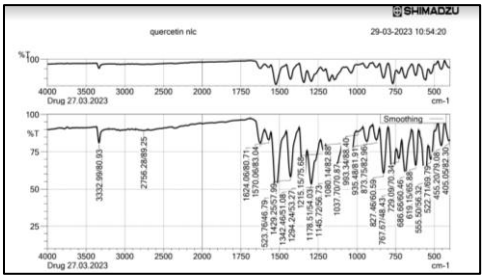
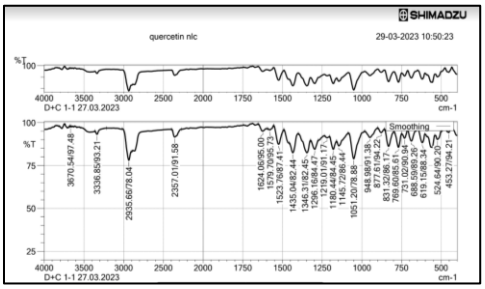


Figure No 2



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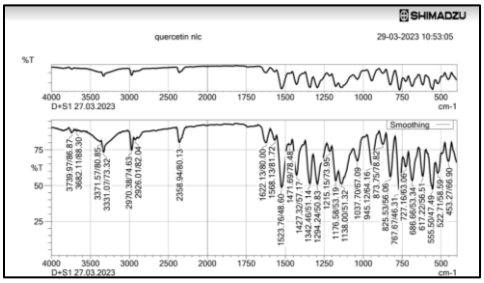

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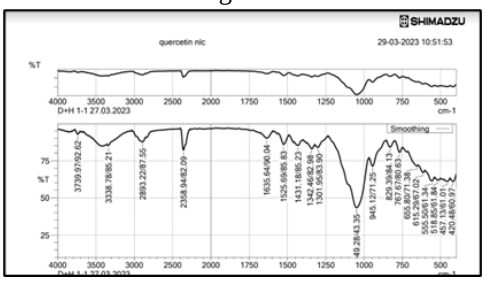


Figure No 5

c. *Determination of the absorption maxima*

((λ max) drug: - A concentration of 10µg/ml was prepared from a standard Piroxicam solution scanned by a UV-visible spectrometer in the range of 200-400 nm using 7.4 PBS as blank then the maximum wavelength (λ max) was determined. It is observed in Figure no 6

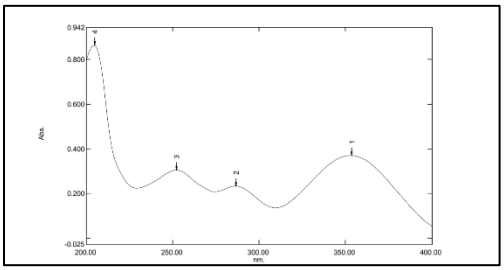


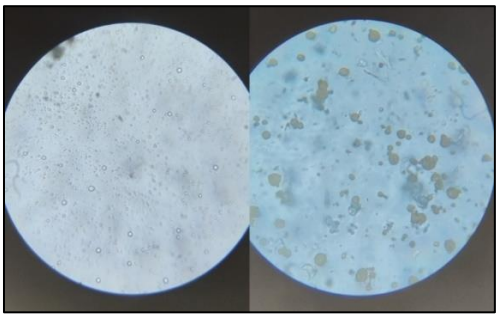
Figure No 6

B. Characterization of Proniosomal Suspension

a. Vesicle size and shape

By optical microscope

Proniosomal suspension (0.1g) of optimized formulation F3 was sonicated for roughly 2 minutes after being mixed using phosphate buffer pH 7.4 (10 ml). Using an optical microscope with magnification powers of 10X and 45X, a sample was placed on a glass slide, the shape of the vesicles was measured, and pictograms were recorded in figure no 7



A B

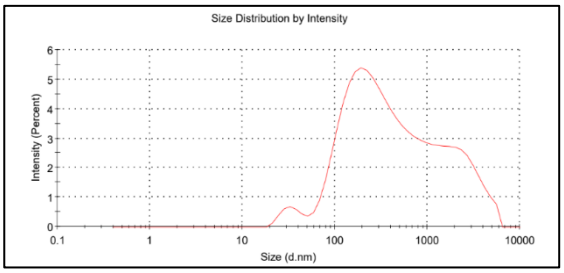
F3 Optimized Formulation

Figure no 7 A (without drug) B (Entrapped Drug)

b. Measurement of Vesicle Size

Figure 8 illustrates the distribution of particle sizes profile of proniosomal suspension (Particle size d. nm vs intensity%), which was determined to be 266.9 nm. Polydispersity index (PI) values, where a lower value indicates greater size uniformity, are used to quantify the uniformity of vesicle size. The dispersion is more homogenous and monodisperse the lower the PI value. A measure of the uniformity of proniosomes size within the formulation, the polydispersity index (PI) value was PI= 0.526.

Figure No 8



c. By Scanning Electron Microscope (SEM)

SEM was used to determine the surface morphological characteristics of formula F3 nanosized vesicles at two different magnifications (5.00 K X, and 1.00 K X). These drug carriers have vesicular characteristics that generate two layers. The organization of the lamellar structure encasing the drug molecules and the shape of the vesicles were both revealed by SEM.

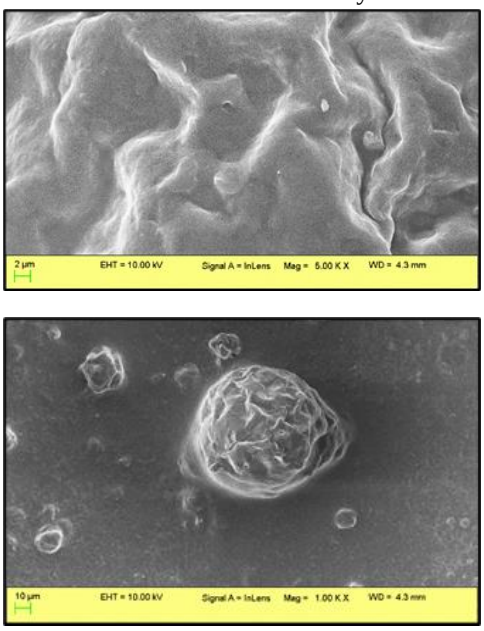


Figure No 9

d. Determination of Zeta Potential

According to Figure 10, the formulation F3 that underwent zeta potential investigation had a zeta value of 1.57 mV, which represents the proniosomes' net charge. The vesicles are stable because there is enough electrostatic repulsion between them due to the high surface charge, which prevents aggregation.

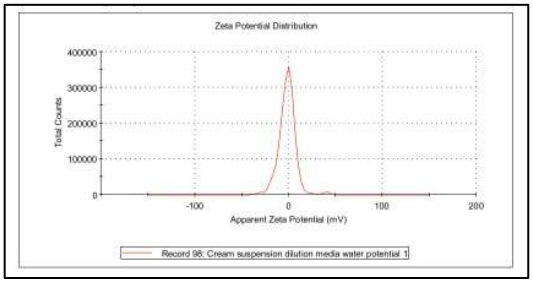


Figure no 10

e. Entrapment Efficiency

Centrifugation-based evaluation of entrapment effectiveness. The longer alkyl chain length of surfactant Span 60 is anticipated to result in improved vesicle entrapment efficiency. The F3 formulation, which may contain the ideal surfactant cholesterol ratio to enable a high entrapment of Piroxicam, demonstrated the maximum entrapment efficiency of 95.40%0.20. The Entrapment Efficiency of all the formulation is depicted below in the table no 3

Formulation Code	Entrapment Efficiency %
F1	85.54%±0.78
F2	82.30%±0.33
F3	95.40%±0.20.
F4	80.22%±0.30
F5	79.25%±1.20
F6	72.54%±0.11

Table no 3: - Entrapment Efficiency of all the formulation

C. Characterizaion of Proniosomal Buccal Film

a. Appearance:- The physical appearance and flexibility were noted visually, for all the films from F1 to F6 were creamish yellow in color, smooth, homogeneity and elegant in appearance

b. Weight variation: The weight of mucoadhesive buccal film was measured using a digital weighing balance, and it was discovered that the average weight of all the films (F1 to F6) fell between 60 and 80 mg.

Formulation Code	Weight Variation (mg)
F1	65.50±0.32
F2	69.40±0.44
F3	73.20±0.51
F4	69.40±0.23
F5	70.30±0.10
F6	72.40±0.33

Table no 4 Weight Variation

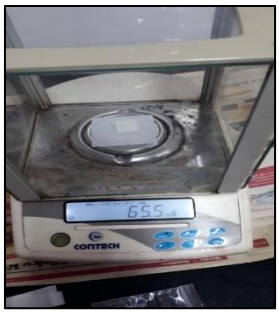


Figure no 11

c. Thickness of the film

The digital micro-meter screw gauge was used. The average thickness of all the films ranges from 0.0754±0.001 to 0.137±0.001 mm.

Formulation Code	Thickness (mm)
F1	0.754±0.001
F2	0.119±0.001
F3	0.137±0.001
F4	0.129±0.002
F5	0.131±0.001
F6	0.089±0.003

Table no 5 Thickness of film

Figure no 12

d. Folding Endurance

All mucoadhesive buccal films have a standard folding endurance value that ranges from 136 to 208. The values were at their best to show excellent buccal film characteristics. The highest folding endurance value is shown by Formulation F3, while the lowest folding endurance value is shown by Formulation F2.

Formulation Code	Folding Endurance (folds)
F1	181±1.52
F2	163±1.03
F3	208±2.00
F4	136±3.02
F5	189±0.57
F6	156±2.08

Table No 6 :- Folding Endurance of the film

e. Mucoadhesive Strength

The Mucoadhesive strength of the formualtion ranges from 2. To 8.55. The formulation F5 shows the lowest mucoadhesive strength and the formualtion F3 shows the highest mucoadhesive strength.

Formulation Code	Mucoadhesive strength
F1	5.4±0.5
F2	3.40±0.06
F3	8.55±0.75
F4	8.1±0.03
F5	2.6±0.2
F6	4.2±0.1

Table no 7 Mucoadhesive Strength

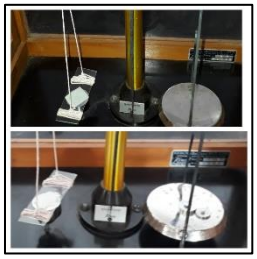


Figure no 13

f. Surface pH

The pH metre was used to measure the surface-pH close to the mucoadhesive buccal film's surface. After allowing time for equilibration, it was discovered that the surface-pH of all films ranged from 6.61 to 6.73 pH (n=3). All formulation batches display pH values within the neutral range, which suggests that there are no cases of buccal discomfort.

Formulation Code	Surface pH
F1	6.62
F2	6.32
F3	6.67
F4	6.61
F5	6.70
F6	6.73

Table no 8 Surface pH

Figure no 14

g. Swelling Index

All formulations' swelling indices were tested. The film's swelling index readings range from 14.09 to 40.22 Formulation F1 had the highest swelling index

Formulation Code	Swelling Index
F1	40.22±1.04
F2	35.10±1.22
F3	20.21±1.32
F4	18.22±0.39
F5	16.22±0.71
F6	14.09±0.41

Table no 9 Swelling Index of the films

h. Drug Content

For all of the formulationsF1 to F6, the drug content percentage was found to be between 84.08% and 95.09% by percentage (01.44% to 1.24%).The findings show that the medicine is evenly dispersed in all film preparations and is going to deliver the medication dose precisely.

Formulation Code	Drug Content (%)
F1	89.12%±0.53
F2	90.21%±0.24
F3	95.09%±1.24
F4	81.35%±0.44
F5	87.05%±0.51
F6	84.085±1.44

Table no 10:- Drug content in all the buccal films

i. % Moisture Loss

All formulas from F1 through F6 had their percent moisture loss determined. The range of 1.44 to 2.88 was found for the average moisture loss percentage. Every formulation exhibits moisture loss within acceptable ranges, which supports the film's resistance to microbiological development.

Formulation Code	% Moisture Loss
F1	2.32%±0.22
F2	2.28%±0.12
F3	1.44%±0.22
F4	1.53%±0.01
F5	1.83%±0.42
F6	2.88%±0.46

Table no 11:- % Moisture loss of all films

j. *In vitro* Residence time

All formulations from F1 to F6 had their invitro-residence times examined for film ranges from 1.32 to 4.28. All of the films' in vitro residence showed favourable swelling and drug release characteristics.

Formulation Code	*In vitro* Residence time
F1	4.01±0.03
F2	3.21±0.01
F3	4.28±0.02
F4	3.11±0.10
F5	2.22±0.48
F6	1.32±0.21

Table no 12:- *In vitro* residence time

k. *In vitro* drug release

Piroxicam mucoadhesive buccal film in vitro dissolving research was completed in pH 7.4 PBS. Calculated drug release from F1 through F6 was plotted on a graph.

	Cumulative Drug release%					
Time	F1	F2	F3	F4	F5	F6
15min	1.33%	4.43%	1.24%	1.32%	1.43%	2.89%
30min	8.45%	8.54%	7.32%	8.32%	5.32%	9.34%
45min	15.34%	16.54%	16.45%	18.89%	15.21%	16.37%
1hr	25.22%	28.32%	29.21%	28.63%	23.36%	32.89%
2hr	49.43%	44.32%	58.32%	49.67%	49.20%	48.32%
4hr	53.65%	58.32%	69.32%	57.87%	59.36%	56.34%
6hr	69.45%	66.43%	75.45%	65.35%	68.65%	69.89%
8hr	78.43%	74.89%	81.25%	75.65%	70.76%	73.43%
12hr	85.39%	82.32%	90.89%	85.31%	84.67%	88.90%
24hr	91.43%	90.21%	95.26%	93.52%	91.32%	92.45%

Table no 13:- *In vitro* drug release

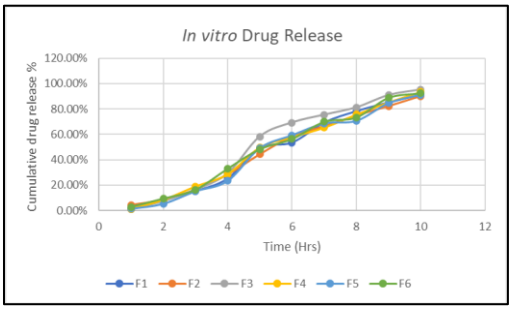


Figure no 15:- Graphical representation of *In vitro* drug release

I. *Ex vivo* permeation Studies

Due to acceptable *in vitro* drug release, *in vitro* diffusion, and mucoadhesive tests, the formulation F3 was chosen as the best for the *ex-vivo* permeation investigations. The results of the drug permeation from the mucoadhesive buccal film containing backing layer acting as a patch providing unidirectional drug release of piroxicam through the goat buccal mucosa show that the drug was released from formulation and permeated through the goat buccal membrane and therefore can possibly be permeated through the human buccal membrane.

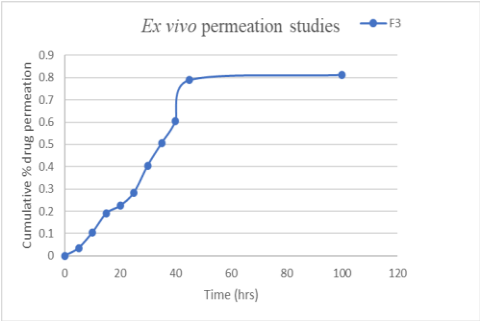


Figure no 16:- *Ex vivo* permeation studies

IV CONCLUSIONS

Due to substantial first-pass metabolism, buccal distribution is a desirable alternate route for the administration of medications with low bioavailability. The results of the numerous trials could be used to draw the next conclusion. There was no interaction between the medication and excipients, according to FTIR measurements. The solvent casting method can be used to make the mucoadhesive buccal film incorporating backing layer, which functions as a patch giving unidirectional drug release of Piroxicam. Mucoadhesive polymers like HPMC E15 and HPMC E4 can be used in this process. The created films had a homogeneous weight, thickness, and drug content as well as good folding endurance. They also had a smooth, flexible, and attractive appearance. All formulations' physicochemical characteristics were found to be within acceptable bounds. All formulations had appropriate salivary pH (5.8 to 7.4) on their surfaces. F3 outperforms the other formulations in terms of drug content, mucoadhesive characteristics, and drug release. Therefore, the F3 batch is regarded as an optimised formulation. Ex-vivo permeation tests for an optimised batch were performed, and the drug penetration results were adequate. Ex-vivo permeation investigations on goats showed that piroxicam may pass through the goat's buccal membrane. Thus, the current investigation comes to the conclusion that Piroxicam could be administered via the buccal route.

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