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FORMULATION AND EVALUATION OF KETOROLAC MUCOADHESIVE BUCCAL TABLETS

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Abstract:

The main objective of present work is formulation and evaluation of ketorolac mucoadhesive buccal tablets. The buccal tablets were tested for weight uniformity, thickness, friability and hardness. Tablets were then evaluated for their swelling index, in vitro drug release, mucoadhesion time (wash-off time) and ex vivo drug permeation. The kinetics and mechanism of the drug permeation through the excised buccal tissue of goat from the buccal tablets were also characterized. The data collected were then analyzed using software to determine the effects of each parameter. The effects of the various parameters involved were then interpreted. The best polymer composite was selected from the various ratios of the polymers. The mucoadhesive strength of buccal tablets increases as the concentration of secondary polymer increases. The above polymer composite had shown satisfactory results in the parameters such as thickness, hardness, drug content, swelling index, mucoadhesive time, in-vitro dissolution and in-vitro diffusion. The satisfactory formulation shows a zero order drug release profile depending on the regression value and shown a satisfactory dissolution profile. The oral cavity and its highly permeable mucosal tissues have been taken advantage for decades as a site of absorption for delivery of drugs to the systemic circulation. So the formulations which target the oral cavity through buccal mucosa are of considerable interest to improve the bioavailability and reduce the frequency of administration of APIs. Drugs administered through the buccal route have a rapid onset of action and leads to improved bioavailability of drugs. The buccal route can by pass the first-pass metabolism, by pass contact of the drugs with the gastrointestinal fluids and paves way for easy access to the membrane sites so that the delivery system can be applied, localized and removed easily. Furthermore, there is good potential for prolonged delivery through the mucosal membrane within the oral mucosal cavity. Buccal adhesive systems offer innumerable advantages in terms of accessibility, administration and withdrawal, retentivity, low enzymatic activity, economy and high patient compliance.

Keywords: *Drug, Evaluation, Metabolism, Bioavailability, Swelling index.*

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INTRODUCTION:

Buccal drug delivery is a favorable route compare to parenterals, injectable andadds a several advantages over other routes. The parenteral route offers excellent bioavailability, similarly having poor patient compliance, anaphylaxis, and some other infections. Peroral route possess some inconvenience to patients. Hence for the immediate release of medication and for instant release at desire location in which the drug is absorbed distributer and easily metabolized. This limitation leads to the development of alternative routes of administration. Buccal mucosa has absorptive function and offers many benefits like avoidance of first pass effect, which is a non-invasive route, increase in bioavailability, a rapid action is possible and reduce side effects. Buccal, sublingual, palatal and gingival regions shows effective drug delivery in oral cavity. Buccal tabets can be administered in the oral cavity as shown in Fig.1. Buccal and sublingual route of drugdelivery aremost widely in which local and systemic effects are treated. The permeability of oral mucosa denotes the physical nature of the tissues. The permeable part is sublingual mucosa and buccal mucosa is thinner part and in which there isa high blood flow and surface area; it is a feasible site when a rapid onset of action is desired. For the treatment of acute disorders sublingual route is a preferred one; however its surface washed with saliva which makes formulations in the oral cavity hard in nature.

Buccal drug delivery system is well accepted because it is having several advantages. Buccal areas offer a control release system which is having immobile surface. The buccal layer is tolerate to potential allergens and has capability of preventing damage compare to other mucosal tissues. In treatment of the local or systemic therapies, buccal mucosa favors a useful measure by overcoming drawbacks and as convenient route for the administration.

This type of route is well vascularized draining to the heart unswervingly via the internal jugular vein.
In chronic systemic therapies buccal drug delivery acts as potential site and chemical modification due to salivary production and its composition. There is a chance of drug loss at site of absorption in case of the oral route and for some dosage form salivary scavenging is constant with in oral cavity which make difficult for retaining to an extensive duration at the site to enhance the absorption. Bioadhesive polymers have prolonged contact time with the tissues and can notably maintain the performance of several drugs. The controlled drug delivery products have high patient compliance and a low cost with enhanced bioavailability.

The unique environment of the oral cavity offer sits potential as a site for drug delivery. Through this route it is possible to realize mucosal (local effect) and transmucosal (systemic effect) drug administration. In the first case, the aim is to achieve a site-specific release of the drug on the mucosa, whereas the second case involves drug absorption through the mucosal barrier to reach the systemic circulation. Therapeutic agents administered through buccal mucosa enters directly to the systemic circulations and thereby circumvent the first pass hepatic metabolism, gastric irritation and other problems associated with conventional oral route.

Advantages

a. It is richly vascularised and additional reachable for administration and removal of formulations.
b. Patient accessibility is high.
c. Retentive dosage forms are suitable for administration.
d. Improves bioavailability by eliminating first passm etabolism.
e. Surface of buccal mucosa achieves a fast cellular recovery.
f. Low enzyme activity.
g. Non-invasive method of drug administration.
h. Ability to incorporate permeation enhancer in the formulation.

Mucoadhesive drug delivery system is now-a-days a booming field for research interest.These are delivery systems, which utilize the property of bioadhesion of certain polymers. Mucoadhesive buccal drug delivery systems offer many advantages over conventional systems such as ease of administration, be promptly terminated in case of toxicity by removing the dosage form from buccal cavity and it is also possible to administer drugs to patients who cannot be dosed orally via this route. Recently much attention has been focused on the design and evaluation of buccal drug delivery systems keeping in view their potential for future market. Therefore a buccal drug delivery system needs to be developed and optimized. 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 a unidirectional way in the mucosa. The unique

environment of the oral cavity offers its potential as a site for drug delivery. Through this route it is possible to realize mucosal (local effect) and transmucosal (systemic effect) drug administration. In the first case, the aim is to achieve a site- specific release of the drug on the mucosa, whereas the second case involves drug absorption through the mucosal barrier to reach the systemic circulation. Therapeutic agents administered through buccal mucosa enters directly to the systemic circulations and thereby circumvent the first pass hepatic metabolism, gastric irritation and other problems associated with conventional oral route.

Mucoadhesive drug delivery system interact with the mucus layer covering the mucosalepithelial surface, & mucin molecules & increase the residence time of the dosage form at thesite of the absorption as depicted in Fig.2. Mucoadhesive drug delivery system is a part of controlled delivery system.

Several theories have been put forward to explain the mechanism of polymer–mucus interactions that lead to mucoadhesion. To start with, the sequential events that occur during bioadhesion include an intimate contact between the bioadhesive polymer and the biological tissue due to proper wetting of the bioadhesive surface and swelling of the bioadhesive as shown in Fig.3. Following this is the penetration of the bioadhesive into the tissue crevices, interpenetration between the mucoadhesive polymer chains and those of the mucus. Subsequently low chemical bonds can become operative. Hydration of the polymer plays a very important role in bioadhesion. There is a critical degree of hydration required for optimum bioadhesion. If there is incomplete hydration, the active adhesion sites are not completely liberated and available for interaction. On the other hand, an excessive amount of water weakens the adhesive bond as a result of an overextension of the hydrogen bonds. During hydration; there is a dissociation of hydrogen bonds of the polymer chains. The polymer–water interaction becomes greater than the polymer-polymer interaction, thereby making the polymer chains available for mucus penetration. Following polymer hydration intermingling between chain segments of the mucoadhesive polymer with the mucus occurs.

MATERIALS AND METHODS:

Formulation of mucoadhesive buccal tablets

Ketorolac mucoadhesive tablets were prepared by direct compression method as per the formulations as shown in Table 1. Before direct compression, all the ingredients were shifted through sieve No. 40 and then thoroughly blended in glass mortar and pestle. Blending was carried out separately for core tablet (polymer and drug) and backing layer (ethylcellulose). The Mixture of core tablet was lubricated with magnesium stearate and talc which was already passed through sieve 60. At first, the core tablets were compressed by using compression machine with 8 mm punch. Then, one compressed core tablet was placed indie cavity manually. Over it, accurately weighed 50 mg of ethyl cellulose was added to each die cavity. It was then leveled and compressed again to obtain Ketorolac buccal tablets having one sided backing layer of ethyl cellulose. After compression, the tablets were weighed to check that it lies within the range of 100±10 mg.

Table 1. Formulation ingredients of Buccal Tablets

F. code	F1	F2	F3	F4	F5	F6
Drug (mg)	10	10	10	10	10	10
Carbopol 934 (mg)	14.5	12	18	14.5	12	18
PVP K30 (mg)	-	-	-	18	24	21.5
Xanthan gum (mg)	18	24	21.5	-	-	-
Sodium lauryl sulphate (mg)	2	2	2	2	2	2
Mg stearate (mg)	1	1	1	1	1	1
Talc (mg)	1	1	1	1	1	1
Backing Layer						
Ethyl Cellulose (mg)	50	50	50	50	50	50

RESULT AND DISCUSSION:

Calibration curve

The calibration curve of drug in the concentration range of 0-12 µg/ml at 322 nm and the result is shown in table and in fig. below.

Table 2. Calibration curve of Ketorolac in pH 6.8

S. No.	Concentration (µg/ml)	Absorbance at 322 nm
1	2	0.087
2	4	0.16
3	8	0.299
4	10	0.45
5	12	0.591

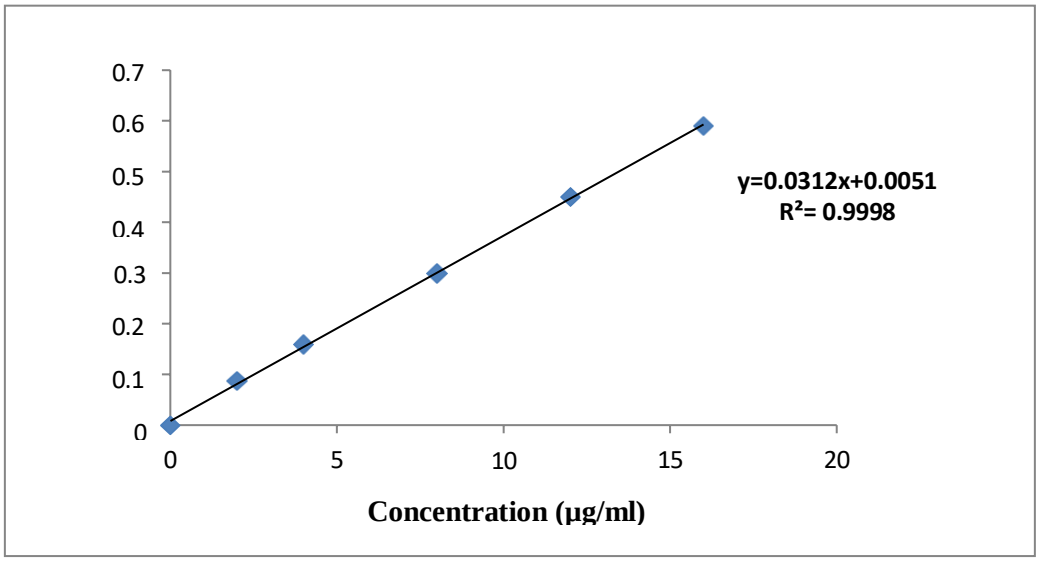

Fig. 1. Calibration curve of Ketorolac in Phosphate buffer pH 6.8

Compatibility study by FTIR

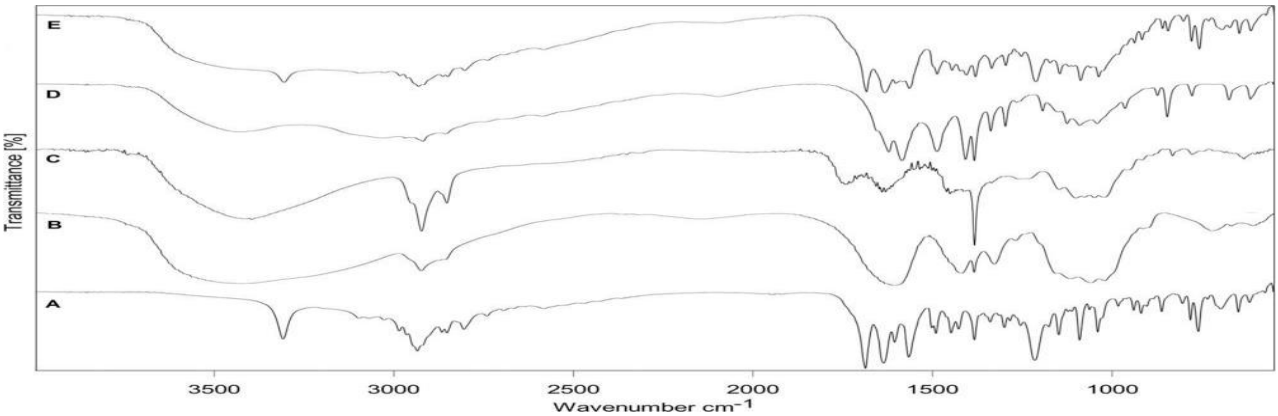

Fig. 2 FTIR spectra of A. Ketorolac; B. PVP K30; C. Xanthan gum; D. physical mixture of Ketorolac, carbopol and PVP 30; E. physical mixture of Ketorolac, carbopol and xanthan gum

Table 3. FTIR Interpretation

Characteristic functional group	Peaks
-OH stretching	3,200cm^{-1}
-COO-stretching	1,417cm^{-1}
-COO-stretching	1,613cm^{-1}
C-O stretching	1,025cm^{-1}
C=O stretching	1,699cm^{-1}
C-F stretching	1,025cm^{-1}
C-N stretch	1,192cm^{-1}

Evaluations of Tablet

Uniformity of Weight:

The results for the uniformity of weight are given in table 4.

Table 4. Uniformity of Weight

S. No.	Formulation code	Weight uniformity (mg)
1.	F1	101.2 ± 4.62
2.	F2	99.3± 4.32
3.	F3	98.8 ± 2.91
4.	F4	97.2 ± 3.16
5.	F5	102.2 ± 4.02
6.	F6	101.1 ± 3.81

Thickness

The results for the thickness of the Ketorolac buccal tablets are given in table 5.

Table 5. Average thickness of the Ketorolac buccal tablets

S. No.	F. code	Thickness (mm)
1.	F1	2.87± 0.091
2.	F2	2.51± 0.067
3.	F3	2.072± 0.08
4.	F4	2.66± 0.051
5.	F5	2.54± 0.023
6.	F6	2.71± 0.053

Hardness

The results for the hardness of the Ketorolac buccal tablets are given in Table 6.

Table 6. Average hardness of the Ketorolac buccal tablets

S. No.	Formulation code	Avg. hardness (kg/cm^2)
1.	F1	3.15± 0.23
2.	F2	3.77 ± 0.18
3.	F3	3.54 ± 0.52
4.	F4	4.02 ± 0.09
5.	F5	3.63 ± 0.55
6.	F6	3.81± 0.11

Friability

The results for the friability test for the Ketorolac buccal tablets are given in table 7.

Table 7. % Friability of the Ketorolac buccal tablets

S. No.	Formulation code	Friability (%)
1.	F1	0.175±0.36
2.	F2	0.034±0.21
3.	F3	0.136±0.85
4.	F4	0.459±0.09
5.	F5	0.042±0.11
6.	F6	0.62±0.10

Surface pH

The results for the surface pH of the Ketorolac buccal tablets are given in table 8.

Table 8. Surface pH of the Ketorolac buccal tablets

S. No.	Formulation code	Surface pH
1	F1	6.87± 0.05
2	F2	6.76± 0.10
3	F3	7.03± 0.02
4	F4	6.81± 0.05
5	F5	6.74± 0.01
6	F6	6.88± 0.21

Swelling Index

The swelling index of the various buccal formulations are given in table 9.

Table 9. Swelling index (%) of the Ketorolac buccal tablets

F. Code	Time (h)					
	1	2	3	4	5	6
F1	5.66±1.11	9.61±0.77	15.03±0.67	19.54±1.12	23.44±0.45	26.2±0.31
F2	11.39±1.09	19.62±0.87	27.82±0.99	36.32±1.33	44.75±0.96	51.48±0.14
F3	7.88±0.91	12.27±0.99	18.68±1.12	21.22±0.63	26.55±1.19	33.72±1.23
F4	7.03±0.87	11.42±0.78	16.64±0.99	19.85±0.76	24.87±0.67	29.33±1.121
F5	12.04±0.75	22.32±1.22	31.68±1.11	39.42±0.54	47.03±0.79	53.55±0.51
F6	8.56±0.91	13.21±2.01	19.82±1.23	25..27±1.45	34.53±0.61	47.86±0.66

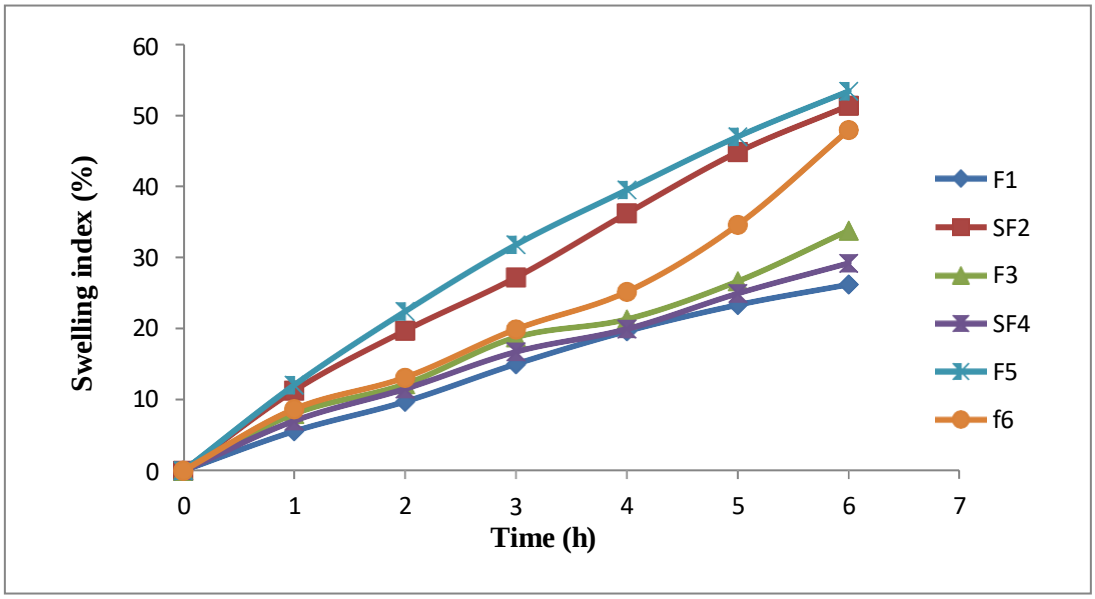

Fig. 3 Swelling index (%) for all formulations

Mucoadhesive time (Wash-off test)

The data from the Wash off test are tabulated in table 10.

Table 10. Time duration of attachment of the Ketorolac buccal tablets

S. No.	Formulation code	Mucoadhesive time
1.	F1	>6 h
2.	F2	5 h 38 min
3.	F3	5 h 49 min
4.	F4	>6h
5.	F5	5 h 31 min
6.	F6	5 h 45 min

Invitro drug release study

The data obtained from the invitro drug release study are represented in table 13 for formulations F1, F2, F3 and in table 14 for formulation F4, F5, F6. The in-vitro dissolution profile for the various Ketorolac buccal tablet formulations is given below in Fig.

Table 11. Cumulative percentage in-vitro drug release of Formulations F1, F2, F3

Time (min)	F1	F2	F3
15	10.22±0.77	15.31±0.54	11.59±0.66
45	23.13±0.56	26.79±0.34	21.88±0.15
60	30.53±0.65	41.37±1.22	36.63±2.02
120	40.03±0.97	62.71±1.34	55.35±1.01
180	51.34±0.78	76.68±0.17	67.49±0.81
240	66.52±0.51	83.32±0.19	70.51±0.14
300	74.55±0.18	93.41±0.99	74.04±0.22
360	78.44±0.88	98.45±0.23	83.30± 0.12

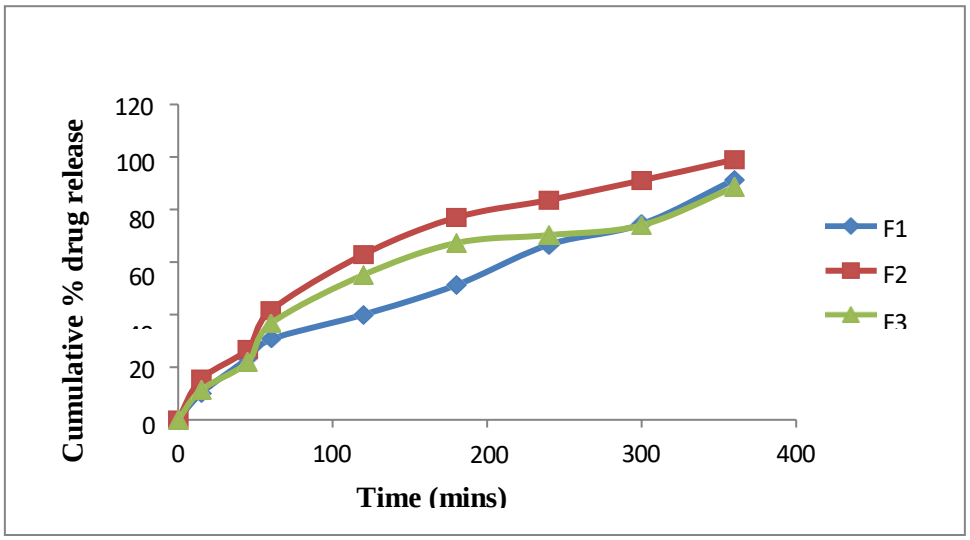

Fig. 4 Invitro dissolution profiles of Formulations F1, F2, F3

Table 12. Cumulative percentage in-vitro drug release of Ketorolac buccal tablet formulations F4, F5, F6

Time (min)	F4	F5	F6
15	15.77±1.22	14.38±1.34	12.41±0.79
45	23.32±1.34	29.31±1.77	25.62±0.56
60	41.53±0.36	55.51±0.99	46.77±1.11
120	52.79±1.91	74.72±2.01	61.66±1.04
180	61.64±0.87	80.86±1.31	75.32±0.67
240	72.72±0.48	91.63±0.22	77.61±1.22
300	77.82±0.53	93.41±1.23	81.53±0.33
360	81.64±0.65	96.64±0.88	87.32±1.04

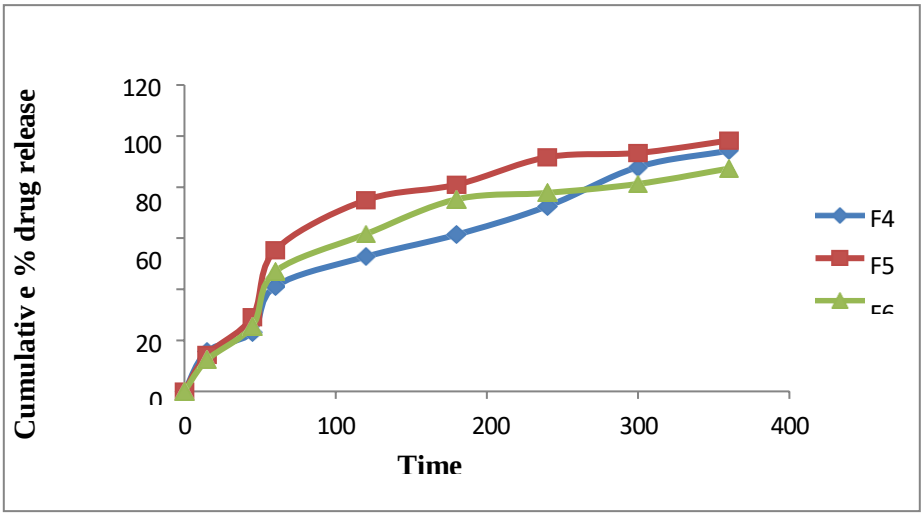

Fig. 5 Invitro dissolution profiles of Formulations F4, F5, F6

Ex-vivo drug permeation study

The drug permeation data for the various Ketorolac buccal tablet formulations is given below in table15 for formulation F1, F2, F3 and in table 16 for formulations F4, F5, F6. The exvivo drug permeation profile for the various Ketorolac buccal tablet formulations is given below in Fig. 22 for formulation F1, F2, F3 and in Fig. 23 for formulations F4, F5, F6**.**

Table 13. Cumulative percentage drug permeation for Ketorolac buccal tablet formulations F1, F2, F3

Time (min)	F1	F2	F3
15	8.73±1.28	11.50±1.22	7.22±1.24
45	20.53±1.45	25.72±0.56	21.03±0.63
60	29.96±1.71	31.10±0.34	30.81±1.05
120	36.43±2.04	49.21±2.01	40.73±1.12
180	47.31±2.11	66.82±1.73	56.91±0.89
240	56.61±0.66	79.92±0.77	60.41±0.67
300	68.22±0.79	83.02±0.225	79.20±0.35
360	72.83±0.71	96.24±0.23	83.85±0.78

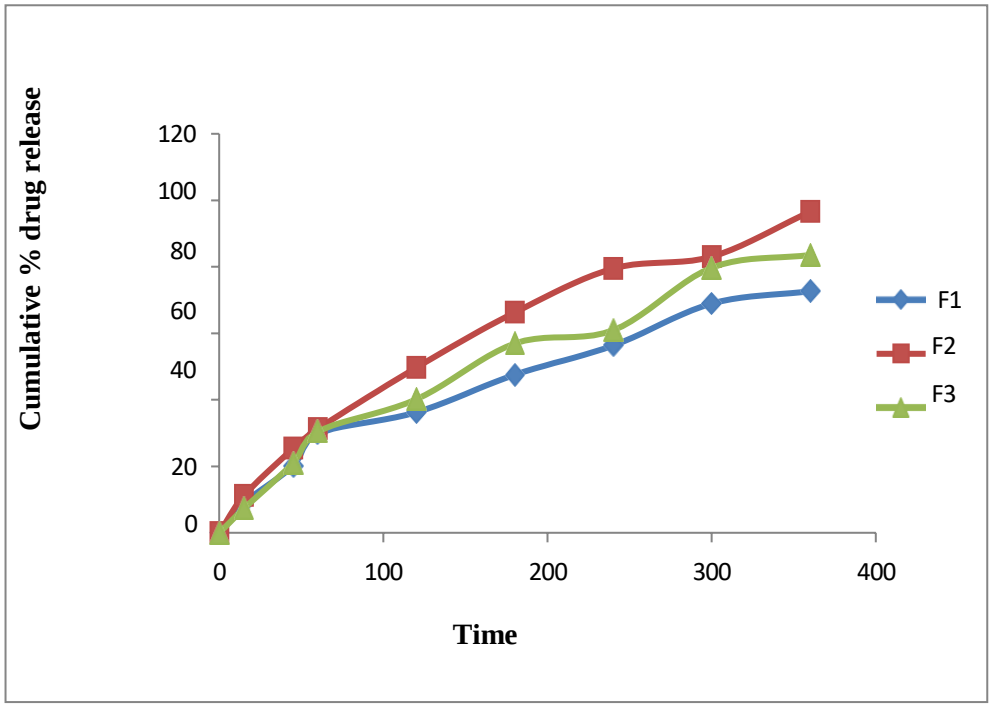

Fig. 6 Ex-vivo diffusion profile of Formulations F1, F2, F3

Table 14. Cumulative percentage drug permeation for Formulations F4, F5, F6

Time (min)	F4	F5	F6
15	9.58±0.64	12.81±1.55	9.47±0.89
45	16.8±1.33	28.52±1.79	17.32±0.78
60	19.35±1.92	36.71±0.89	21.53±1.76
120	28.4±0.91	59.41±0.86	39.92±1.54
180	47.37±0.75	71.59±0.78	53.47±1.03
240	59.7±0.47	82.6±1.27	61.9±1.07
300	70.13±0.59	89.81±1.11	74.79±0.74
360	79.74±1.63	95.11±0.36	81.05±0.97

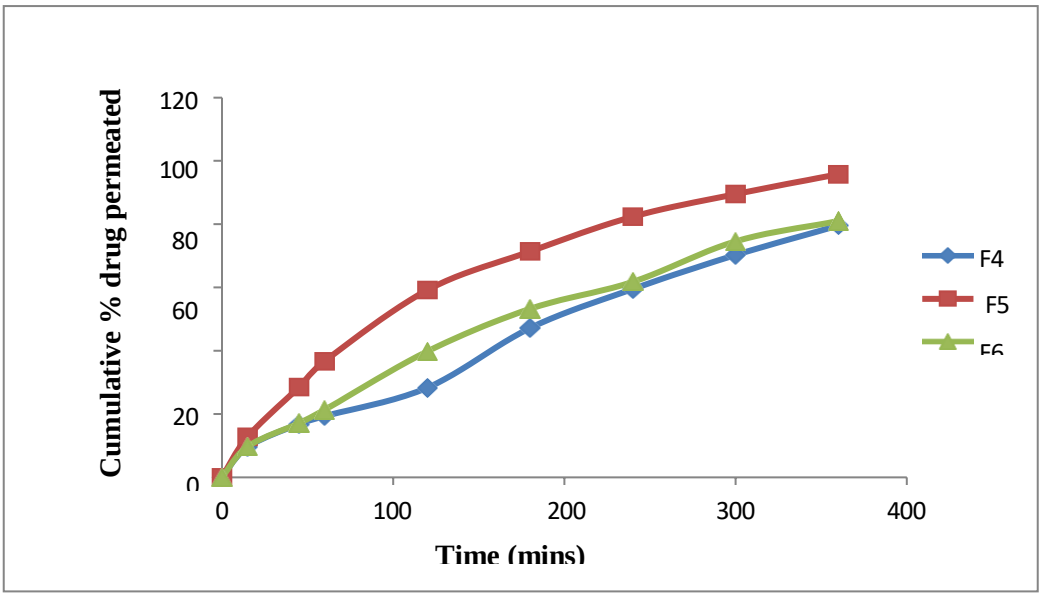

Fig. 7 Ex-vivo diffusion profile of Formulations F4, F5, F6

SUMMARY AND CONCLUSION:

In the present work design efficacious and prolonged release mucoadhesive buccal tablets of Ketorolac was the main objective using various polymers to reduce dosing frequency, decrease gastric irritation and to improve patient compliance.

The buccal tablets were tested for weight uniformity, thickness, friability and hardness. Tablets were then evaluated for their swelling index, in vitro drug release, mucoadhesion time (wash-off time) and ex vivo drug permeation.

The kinetics and mechanism of the drug permeation through the excised buccal tissue of goat from the buccal tablets were also characterized. The data collected were then analyzed using software to determine the effects of each parameter. The effects of the various parameters involved were then interpreted.

The best polymer composite was selected from the various ratios of the polymers. The mucoadhesive strength of buccal tablets increases as the concentration of secondary polymer increases. The above polymer composite had shown satisfactory results in the parameters such as thickness, hardness,

drug content, swelling index, mucoadhesive time, in-vitro dissolution and in-vitro diffusion. The satisfactory formulation shows a zero order drug release profile depending on the regression value and shown a satisfactory dissolution profile. Slow, controlled and maximum release of Ketorolac over a period of 6 h was obtained from buccal tablets F2 formulation.

The oral cavity and its highly permeable mucosal tissues have been taken advantage for decades as a site of absorption for delivery of drugs to the systemic circulation. So the formulations which target the oral cavity through buccal mucosa are of considerable interest to improve the bioavailability and reduce the frequency of administration of APIs.

Drugs administered through the buccal route have a rapid onset of action and leads to improved bioavailability of drugs. The buccal route can by pass the first-pass metabolism, by pass contact of the drugs with the gastrointestinal fluids and paves way for easy access to the membrane sites so that the delivery system can be applied, localized and removed easily. Furthermore, there is good potential for prolonged delivery through the mucosal membrane within the oral mucosal cavity. Buccal adhesive systems offer innumerable advantages in terms of accessibility, administration and withdrawal, retentivity, low enzymatic activity, economy and high patient compliance.

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