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Development and *In-Vitro* Evaluation of Ketorolac Loaded Mucoadhesive Buccal Tablets

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ABSTRACT

The goal of the current study was to develop mucoadhesive buccal ketorolac tablets with an effective and longer release to reduce dosage frequency, mitigate gastrointestinal pain, and improve patient compliance. Different ratios of two polymer mixtures (Carbopol 943 and PVP K30, as well as carbopol and xanthan gum) were used. The weight, homogeneity, thickness, friability, and hardness of the buccal tablets were measured. Next, the swelling index, in vitro drug release, and muco-adhesion time of the tablets were evaluated (wash-off time). Out of the different polymer ratios, the best polymer composite was chosen. Carbopol 934 and PVP K30 have been discovered to have the optimal polymer ratio of 1:2. The secondary polymer concentration boosts the mucoadhesive power of buccal tablets. In terms of qualities like thickness, hardness, drug content, swelling index, mucoadhesive time, in-vitro dissolution, and in-vitro diffusion, the aforementioned polymer composite has done well. Depending on the regression value, the relevant formulation displays a satisfactory dissolving profile. Buccal tablets F2 formulation with Carbopol 934 and PVP K30 provided a delayed, controlled, and maximal release of ketorolac over a period of six hours.

1. INTRODUCTION

Mucoadhesive Drug Delivery System[1]

The study of mucoadhesive drug delivery methods is becoming more prevalent today. These are all delivery techniques that rely on the bio adhesion properties of a specific polymer. By expelling the dosage form from the buccal cavity in the event of toxic effects, mucoadhesive buccal drug delivery systems have a number of advantages over conventional systems, including easy handling, the ability to administer medication to patients who cannot take oral doses, and the ability to quickly stop treatment.[2] An ideal buccal adhesive system must have the following characteristics: short-term adhesion to the attachment site, controlled pharmaceutical release, and unidirectional mucosal administration of the medicine. Due to its unique environment, the oral cavity may be a good area for administering drugs. This method makes it feasible to mucosally and transmucosally give drugs (for local effects) (for systemic effects).[3]

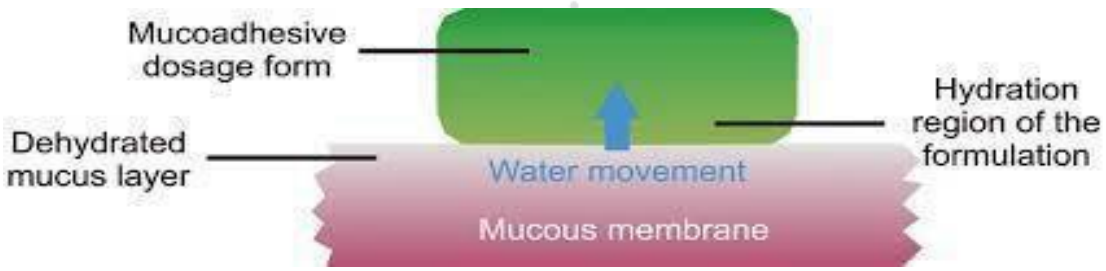

Fig. No. 1. Mucous membrane and mucoadhesive dosage form interaction

Mucoadhesive drug delivery methods make contact with the mucus layer that covers the mucosal epithelial surface and mucin molecules in order to prolong the duration of time the dosage form is in contact with the receptor site, as illustrated in Figure 1. Controlled delivery systems include mucoadhesive medication delivery systems.

Buccal Tablets[4]

Buccal tablets are created similarly to oral tablets with the addition of a muco-adhesive polymer, either of natural origin (tragacanth, guar gum) or synthetic and semi-synthetic origin (carboxy methyl cellulose, poly ethylene glycol).

For buccal tablets, flat, elliptical, or capsule-shaped tablets are frequently utilized since they may be held between the gum and cheek the easiest. The second upper tooth's crown is where the parotid duct empties into the mouth, not far from where buccal tablets are placed. The most often given medications in buccal tablet form includes antiemetics, nicotine for quitting smoking, anti- microbials for treating mouth infections, and hormones for HRT. All of these drugs may be used in extended-release forms.[5]

Types of buccal tablets[6]

The different types of buccal tablets that can be fabricated are:

a) A straightforward monolithic matrix tablet.

b) Water-impermeable matrix tablet with unidirectional drug release

c) Unidirectional matrix tablet with a backing membrane

d) A bi-layered tablet comprising a mucoadhesive polymer layer and a non-adhesive drug reservoir

e) A bi-layered tablet having a drug-containing bioadhesive layer on top and an inert, non- bioadhesive layer underneath.

f) A tablet with three layers: a bottom bioadhesive layer, an upper backing membrane, and a central drug-containing core.

Basic components of buccal mucoadhesive drug delivery system[7,8]

The following are the basic components of a buccal mucoadhesive drug delivery system:

1. Drug substance – Before developing buccoadhesive drug delivery systems, it is important to figure out if the intended action is for immediate or delayed release, as well as for local or systemic impact. Using pharmacokinetic parameters, the best drug should be selected for the design of buccoadhesive drug delivery systems.

2. Bioadhesive polymers: These are vital materials of bioadhesive medication delivery systems. With biological membranes, it should work. It must create strong non-covalent bonding with the mucin/epithelial surface.[9]

3. Backing membrane: The mucous membrane acts as the primary surface to which bioadhesive devices are attached. The backing membrane's components must be safe, impermeable to drugs, and penetration-enhancing. The buccal bioadhesive patches' impermeable layer prevents drug loss and enhances patient compliance. As backing membranes, materials such as carbopol, magnesium stearate, HPMC, etc. are often used.[10]

4. Penetration enhancers. Penetration enhancers are used in buccoadhesive formulations to speed the release of the drug. They facilitate the medicine's systemic dispersion by making it simpler for the material to enter live tissues. Sodium lauryl sulphate, CPC, polysorbate 80, laureth-9, sodium fusidate, polmitoyl carnitine, azone, sodium glycocholate, dimethyl formamide, and others are some of the penetration enhancers that are often used.[11,12]

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)[13, 14]

NSAIDs, sometimes referred as aspirin-like drugs, are among the most commonly prescribed drugs. They provide symptomatic relief from pain and swelling in more severe inflammatory conditions such sports injuries, fractures, sprains, and other soft tissue injuries as well as in chronic joint illnesses like osteo- and rheumatoid arthritis. Additionally, they alleviate the discomfort associated with menstruation, post-operative, dental, headache, and migraine conditions. Since many NSAIDs may be purchased OTC, they are often used for a range of mild aches and pains. Tablets, injections, and gels are some of the available preparations.

A well-known non-steroidal anti-inflammatory drug with strong analgesic qualities is ketorolac (15). It is now used intramuscularly and orally in a range of split doses to temporarily reduce post- operative pain. To treat moderate to severe pain, the medication is taken orally as a daily tablet (10 mg four times a day). ketorolac has a half-life of 4-6 hours. Due to its short half-life, regular dose is necessary to reduce the pain of postoperative patients. Thus, the administration of buccal mucoadhesive tablet may be used as an alternative delivery method.

2. MATERIAL AND METHODS

Ketorolac (API) was received as a free gift sample from Navakar Biochemical, Gujrat. Carbopol 934P, talc and sodium lauryl sulphate was procured from Loba chemicals pvt. Ltd.

Hyderabad. PVP K30 and Magnesium stearate was obtained from Merck limited, Mumbai and all other reagents used were of analytical grade.

Methods/Methodology

1. Pre-compressional Studies

Calibration curve: Preparation of stock solution

10 mg of the drug, which was carefully weighed, was dissolved in phosphate buffer pH 6.8 in a 100 ml volumetric flask to produce a concentration of 100 µ g/ml of ketorolac standard stock solution.

Preparation of standard dilutions

Five 50 ml volumetric flasks were used. The stock solution was divided into aliquots of 1 ml, 2 ml, 4 ml, 6 ml, and 8 ml, which were then diluted to the appropriate amounts to produce the concentrations of 2 µ g/ml, 4 µ g/ml, 8 µ g/ml, 12 µ g/ml, and 16 µ g/ml, respectively. Then, at λmax 322 nm, UV/visible spectrometer was used to analyse it. After taking readings, a potted graph (fig. 2) was made.

2. Drug polymer compatibility study[18]

Infrared spectroscopy was used to examine for any possible interactions between the drug and the bioadhesive polymers being employed. The infrared spectrum was measured using a Shimadzu IR-470 spectrophotometer. The samples were made by applying 6 tonnes of pressure on discs of potassium bromide. The scan area was more than 4000-400 cm-1.

Formulation of mucoadhesive buccal tablets[19]

The direct compression method was used to develop ketorolac mucoadhesive tablets using the formulas shown in Table 1. All ingredients were well combined in a glass mortar and pestle before being passed through sieve No. 40 for direct compression. The base layer and core pills were made from separate batches of polymer and medication (ethyl cellulose). Talc that had previously been sieved through sieve 60 and magnesium stearate were used to lubricate the composition of the core tablets.

The core tablets were first compressed using an 8 mm punch on a compression machine. The die cavity was then manually filled with one crushed core tablet. Then, 50 mg of ethyl cellulose that had been carefully measured was placed over each die cavity. To manufacture ketorolac buccal tablets with an ethyl cellulose backing layer on one side, it was then flattened and compressed once more. To make sure the dose falls between 100 and 10 mg, the pills were crushed, then weighed.

Table 1. Formulations prepared by direct compression method

Formulation code	F1	F2	F3	F4	F5	F6
Core tablet						
Drug(mg)	10	10	10	10	10	10
Carbopol 934 (mg)	18	12	14.5	18	12	14.5
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

Evaluation of the compressed tablets

The above-mentioned batches underwent tests to evaluate their average thickness, average weight, weight variation, hardness, friability, swelling index, surface pH, in vitro drug release, mucoadhesive strength, residence duration, and in vivo bioavailability.

1. Weight variation[20]

Each formulation's 20 tablets were collected. The weight of each pill in the chosen formulations was measured, and the average weight and standard deviation of 20 tablets were calculated.

Table 2. Limits for Tablet Weight Variation

Average weight of tablet	Deviation permitted
80mg or >	±10
80mg-250mg	±7.5
>250 mg	±5

2. Thickness[20]

Vernier callipers were used to gauge the thickness of the manufactured tablets. Each formulation's 20 tablets were collected. Then, 20 pills' average thickness and standard deviation were calculated.

3. Friability

Using the Roche friabilator, the tablets' friability was assessed. 20 pills from each batch were first weighed and put into the friabilator. For four minutes, the friabilator was run at 25 rpm. The tablets were weighed again 4 minutes later. The formula was then used to determine the friability.

$$\text{Friability (\%)} = \frac{\text{initial weight} - \text{final weight}}{\text{Initial weight}} \times 100$$

4. Hardness

For this, a Monsanto hardness tester was employed. Ten pills from each batch were tested for hardness. Next, the standard deviation and average hardness were determined.

5. *In-vitro* swelling studies[22]

Using a 2% w/v agar gel plate, the quantity of edoema connected to mucoadhesive tablets was calculated. Ten pills were weighed for each formulation, and the average weight of the ten tablets was computed (W1). The tablets were then put into petri dishes that had been heated to 370.1°C with the core towards the gel surface. At intervals of 1, 2, 3, 4, 5 and 6 hours, the pills were taken out, the surface water was absorbed using filter paper, and the enlarged tablets were weighed. This method was used to determine the swelling index after the calculation of the average weight (W2).

% Swelling index = [(W2-W1)/ W2] x 100

6. Determination of surface pH of tablets[22]

Each batch's mucoadhesive tablets were allowed to swell on the surface of an agar plate for 2 hours. Using pH paper that was adhered to the swelling tablet's core surface, the surface pH was determined.

7. *In-vitro* release studies[25]

Using a USP type II dissolve test apparatus, the drug release rate from buccal tablets was examined. The dissolving solution was 900 cc of phosphate buffer with a pH range of 6.8-0.5. The release was performed at a temperature of 37°C and a rotating speed of 50 rpm. The backing layer was attached to the glass disc using cyanoacrylate glue since the tablet was only intended to release the drug from one side. The disc was placed at the bottom of the dissolution jar. At regular intervals, fresh medium was added after removing samples (5 mL). A UV spectrophotometer was used to analyze the samples at 322 nm after they were filtered using filter paper.

3. RESULT AND DISCUSSION

3.1 Pre-compressional Evaluations

3.1.1 Calibration curve

In the concentration range of 0-16 g/ml, the drug calibration curve followed Beer Lambert's law (R2 = 0.9994) at 322 nm. The result is displayed in table 3 and the plot is displayed in fig. 2.

Table No. 3. Calibration curve of Ketorolac in pH 6.8

Sr. No.	Concentration (µg/ml)	Absorbance at 322 nm
1	2	0.085
2	4	0.173
3	8	0.284
4	10	0.451
5	12	0.589

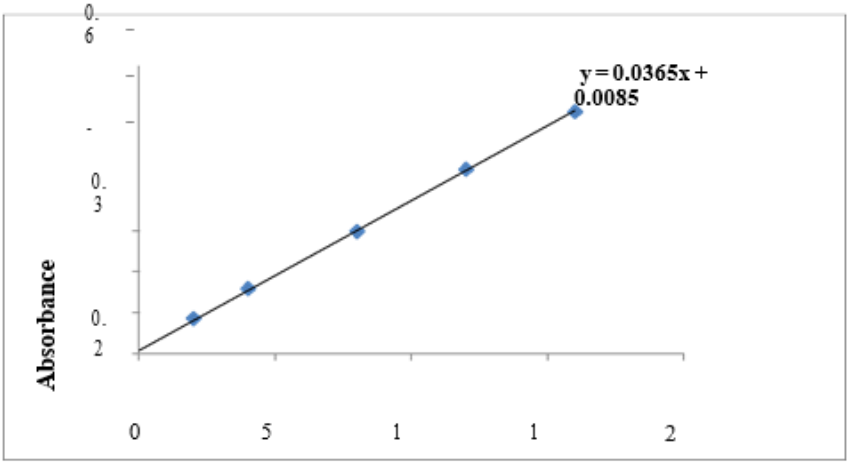

Fig. No. 2. Standard calibration curve of Ketorolac in Phosphate buffer pH 6.8.

3.1.2 Compatibility study by FTIR

The results of the study utilizing FT-IR spectroscopy are shown in Fig. 3. The distinctive peaks of ketorolac are located at 3,058 cm1, 1,644 cm1, 1,533 cm1, 1,350 cm1, 1,130 cm1, 1,350 cm1, the oxazole ring is at 1,350 cm1, the C-F stretching is strong at 1,130 cm1, and the moderate C-N stretching is at the piperidine ring. The C-OH asymmetric stretching at 1,166 cm1, the carbonyl group C=O stretching at 1,699 cm1, and the carboxylic acid -OH stretching at 3,400 to 2,800 cm1 are all clearly seen in the PVP K30 spectrum. The stretching of -OH at a distance of about 3,200 cm1, the stretching of asymmetric and symmetric COO at distances of 1,613 cm1 and 1,417 cm1, respectively, and the stretching of C-O at a distance of 1,025 cm1 all exhibit distinct peaks in the xanthan gum spectrum. Table 4 displays every peak connected to each bond.

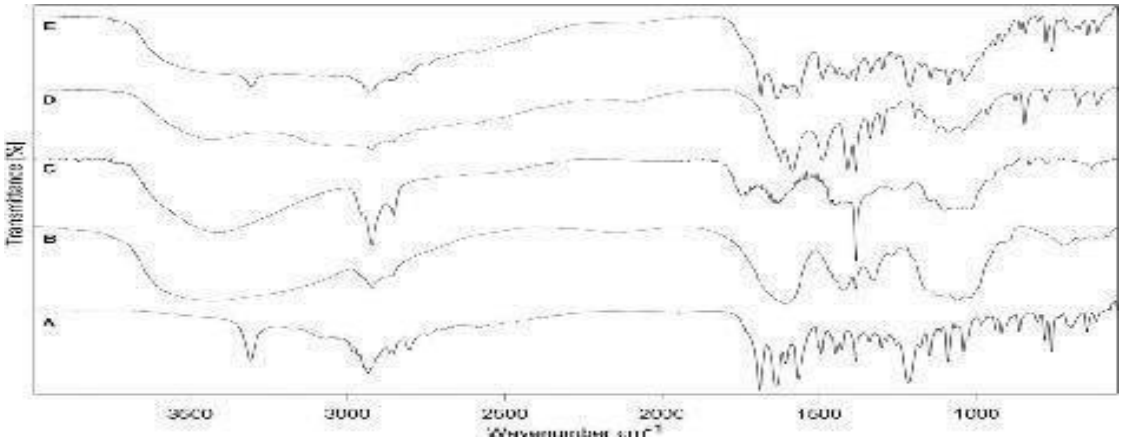

Fig. No. 3. FTIR spectra of (A)-Ketorolac; (B)- PVP K30; (C)- Xanthan gum; (D)- physical mixture of Ketorolac, carbopol and PVP 30; (E)- physical mixture of Ketorolac, carbopol and xanthan gum

Table No. 4. Peaks obtained for various chemical bonds.

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

3.2 Ketorolac - Buccal Tablet Evaluations

3.2.1 Uniformity of Weight:

The results for the uniformity of weight are tabulated in table 5.

Table 5. Uniformity of Weight

Sl. No.	Formulation code	Weight uniformity (mg)
1.	F1	101.1 ± 3.62
2.	F2	99.3 ± 3.32
3.	F3	98.8 ± 1.91
4.	F4	97.4 ± 2.16
5.	F5	102.2 ± 3.02
6.	F6	101.3 ± 2.81

3.2.2 Thickness of the Ketorolac buccal tablet

The results for the thickness of the Ketorolac buccal tablets are tabulated in table 6.

Table 6. Average thickness of the Ketorolac buccal tablets

Sl. No.	Formulation code	Thickness (mm)
1.	F1	2.97 ± 0.091
2.	F2	2.61 ± 0.067
3.	F3	2.082± 0.08
4.	F4	2.76 ± 0.051
5.	F5	2.74 ± 0.023
6.	F6	2.81 ± 0.053

3.2.3 Hardness of the Ketorolac buccal tablets

The results for the hardness of the Ketorolac buccal tablets are tabulated in Table 7.

Table 7. Average hardness of the Ketorolac buccal tablets

Sl. No.	Formulation code	Avg. hardness (kg/cm)
1.	F1	3.25 ± 0.23
2.	F2	3.87 ± 0.18
3.	F3	3.64 ± 0.52
4.	F4	4.03 ± 0.09
5.	F5	3.54 ± 0.55
6.	F6	3.92 ± 0.11

3.2.4 Friability of the Ketorolac buccal tablets

The results for the friability test for the Ketorolac buccal tablets are tabulated in table 8.

Table 8. % Friability of the Ketorolac buccal tablets

Sl. No.	Formulation code	Friability (%)
1.	F1	0.163±0.36
2.	F2	0.026±0.21
3.	F3	0.125±0.85
4.	F4	0.476±0.09
5.	F5	0.032±0.11
6.	F6	0.53±0.10

3.2.5 Surface pH

The results for the surface pH of the Ketorolac buccal tablets are tabulated in table 9.

Table 9. Surface pH of the Ketorolac buccal tablets

Sl. No.	Formulation code	Surface pH
1	F1	6.77 ± 0.05
2	F2	6.87 ± 0.10
3	F3	7.01 ± 0.02
4	F4	6.91 ± 0.05
5	F5	6.84 ± 0.01
6	F6	6.97 ± 0.21

3.2.6 Swelling Index

The swelling index of the various buccal formulations are tabulated in Table 10. The extent of swelling is represented in Fig. 4.

Table 10. Swelling index (%) of the Ketorolac buccal tablets

Formulation code	Time (h)					
	1	2	3	4	5	6
F1	5.55±1.11	9.72±0.77	15.01±0.67	19.63±1.12	23.33±0.45	26.2±0.31
F2	11.28±1.09	19.71±0.87	27.91±0.99	36.21±1.33	44.83±0.96	51.37±0.14
F3	7.99±0.91	12.18±0.99	18.77±1.12	21.31±0.63	26.66±1.19	33.81±1.23
F4	7.01±0.87	11.51±0.78	16.73±0.99	19.94±0.76	24.94±0.67	29.21±1.121
F5	12.06±0.75	22.41±1.22	31.79±1.11	39.51±0.54	47.01±0.79	53.42±0.51
F6	8.67±0.91	13.12±2.01	19.91±1.23	25..18±1.45	34.61±0.61	47.95±0.66

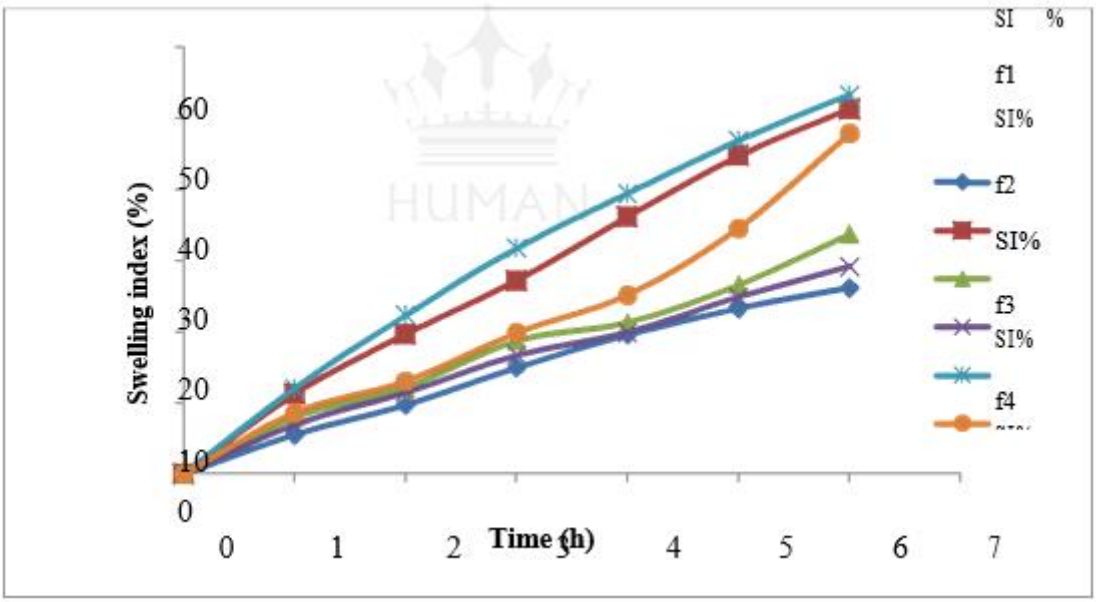

Fig. No. 4. Swelling index (%) for all formulations

3.2.7 Mucoadhesive time (Wash-off test)

The data from the Wash off test are tabulated in table 11.

Table 11. Time duration of attachment of the Ketorolac buccal tablets

Sl. No.	Formulation code	Mucoadhesive time
1.	F1	> 6 h
2.	F2	5 h 36 min
3.	F3	5 h 48 min
4.	F4	> 6h
5.	F5	5 h 32 min
6.	F6	5 h 46 min

3.2.8 *In vitro* drug release study

Tables 12 and 13 for formulations F1, F2, and F3 show the results of the in vitro drug release study, respectively. Figs. 5 and 6 below illustrate the in-vitro dissolving profiles for the various Ketorolac buccal tablet formulations F1, F2, and F3.

Table 12. Cumulative percentage in-vitro drug release of Ketorolac buccal tablet formulations F1,F2,F3

Time (min)	F1	F2	F3
15	11.11±0.77	14.51±0.54	12.39±0.66
45	23.32±0.56	26.79±0.34	21.88±0.15
60	30.62±0.65	41.57±1.22	36.63±2.02
120	40.01±0.97	62.91±1.34	55.15±1.01
180	51.23±0.78	76.98±0.17	67.29±0.81
240	66.61±0.51	83.62±0.19	70.31±0.14
300	74.41±0.18	93.11±0.99	74.05±0.22
360	78.35±0.88	98.24±0.23	84.50± 0.12

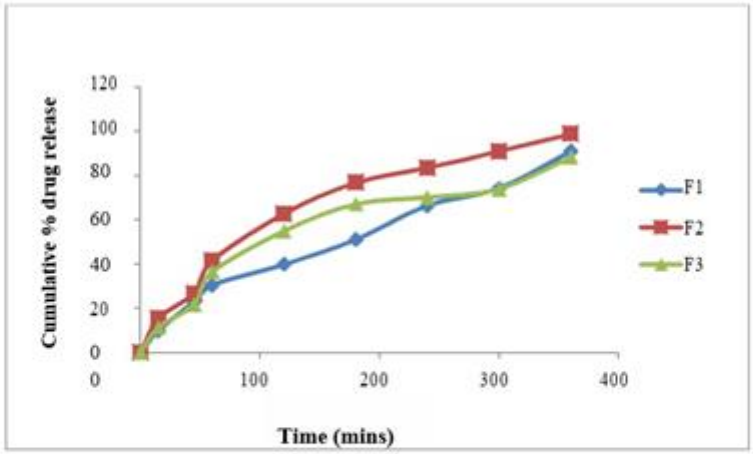

Fig.5 In vitro dissolution profiles of Ketorolac buccal tablet formulations F1 ,F2, F3

Table 13. Cumulative percentage in-vitro drug release of Ketorolac buccal tablet formulations F4,F5,F6

Time (min)	F4	F5	F6
15	14.77±1.22	13.38±1.34	12.42±0.79
45	23.12±1.34	29.11±1.77	25.62±0.56
60	41.23±0.36	55.31±0.99	46.97±1.11
120	52.79±1.91	74.92±2.01	61.66±1.04
180	61.44±0.87	80.96±1.31	75.32±0.67
240	72.52±0.48	91.73±0.22	77.81±1.22
300	77.92±0.53	93.41±1.23	81.33±0.33
360	82.34±0.65	96.53±0.88	88.32±1.04

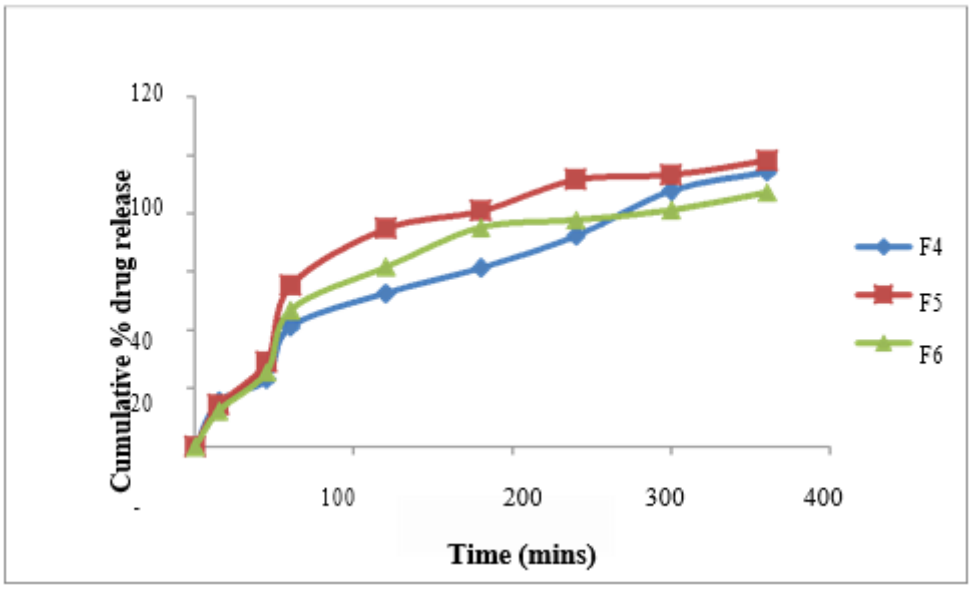

Fig. No. 6: In vitro dissolution profiles of Ketorolac buccal tablet formulations F4, F5, F6

3.3 DISCUSSION

Pre-compressional formulation parameters

The usual calibration of pure medicine proved the pharmacopoeia standards of the ketorolac that was given.

According to the obtained FTIR peaks, there were no significant interactions between the physical combination of the medication ketorolac and the formulation excipients.

Weight variation

Weight fluctuation readings are found to be within the I.P. allowed range for the common oral tablet.

The weights of the tablets varied from 97.3 to 102.1 mg, with a 1.93 to 4.62 mg inaccuracy.

Improper handling of the tablet weights during the punching process is one of the potential causes of the high variance.

Thickness

Ketorolac buccal tablets average thickness is discovered to be very consistent with little fluctuation.

The range of observed tablet preparation thicknesses was 2.60mm to 2.98mm, with a standard variation of between 0.023 and 0.091mm.

To achieve good mucoadhesion, the tablet's thickness and overall weight must be suitable as the dosage form's geometry also affects the mucoadhesive characteristic.

Hardness and friability

The hardness of the manufactured Ketorolac buccal tablet ranges from 3.24 to 4.02 g/cm2, with a standard variation of 0.09 to 0.55.

The friability ranges from 0.025% to 0.520% as well. Friability is less than 1% for any formulation.

Although the buccal Ketorolac tablets are only moderately hard, data on friability indicates that they are quite resistant and may withstand handling in a normal circumstance.

Surface pH

The pH of the tablets' surfaces ranged from 6.58 to 7.01, or close to neutral. If anything, the pH of the tablet's surface has barely altered.

It is assumed that the buccal cavity was not irritated as a result.

Swelling Index

The swelling investigation's findings show that all of the tablets' swelling indices increase over time due to the polymer's slow absorption of water because of its hydrophilicity.

For uniform and extended medication release and efficient mucoadhesion, the mucoadhesive buccal system must exhibit the proper swelling behaviour.

For formulations having carbopol 943 with PVP 30, the swelling index after 6 hours ranges from 16.92 to 41.37%, whereas for buccal tablets containing carbopol 934 with xanthan gum, it ranged from 19.21-43.42%.

The swelling index has a negative relationship with carbopol and a positive relationship with the amount of the second polymer (such as PVP 30 or xanthan gum).

More of the second polymers are included in the formulation with the highest swelling index (PVP K30 and Xanthan gum).

They have a lower viscosity grade, which facilitates water absorption into the matrix of the tablet. They are, therefore, absorbing water more quickly.

In vitro drug release

Each formulation demonstrates superior release, or >85%.

The drug release was seen to vary from 78.35% to 98.24% for formulations F1, F2, and F3 (which contain carbopol and PVP 30).

Contrarily, the drug release for the carbopol and xanthan gum-containing formulations F4, F5, and F6 ranged from 82.34% to 96.53%.

The release of the drug from the tablets is delayed by a greater carbopol content.

Additionally, the formulation with the greatest swelling index demonstrates a significant degree of drug release.

This could be because the polymer matrix swells significantly as a result of the polymers' increased water intake, allowing the medication to diffuse out more quickly.

4 SUMMARY AND CONCLUSION

4.1 SUMMARY

In order to reduce dosing frequency, minimize gastrointestinal discomfort, and improve patient compliance, the current study aimed to create mucoadhesive buccal ketorolac tablets. Different ratios of two polymer mixtures (Carbopol 943 and PVP K30, as well as carbopol and xanthan gum) were used. The weight, homogeneity, thickness, friability, and hardness of the buccal tablets were measured. Next, the swelling index, in vitro drug release, and mucoadhesion time of the tablets were evaluated (wash-off time).

Among the different polymer ratios, the best polymer composite was chosen. Carbopol 934 and PVP K30 have been found to have the optimal polymer ratio of 1:2. The secondary polymer concentration boosts the mucoadhesive power of buccal tablets. In terms of qualities like thickness, hardness, drug content, swelling index, mucoadhesive time, in-

vitro dissolution, and in-vitro diffusion, the aforementioned polymer composite has done well. Depending on the regression value, the final formulation exhibits a good dissolving profile. Buccal tablets F2 formulation with Carbopol 934 and PVP K30 provided a delayed, controlled, and maximal release of ketorolac over a period of six hours.

Future study will be based on long-term pharmacokinetic and pharmacodynamic studies in people to determine its efficacy and safety.

4.2 CONCLUSION

It has long been common practice to provide drugs to the systemic circulation through the extremely permeable mucosal tissues of the mouth cavity. Therefore, formulations that target the oral cavity through the buccal mucosa are of significant interest in order to maximize API bioavailability and minimize API administration frequency.

Drugs administered buccally have a quicker onset of action and a better absorption. The buccal route allows for easy access to membrane sites for the administration, localization, and removal of the delivery system while avoiding first-pass metabolism, pharmaceutical interaction with gastrointestinal fluids, and first-pass metabolism. Furthermore, there is a good likelihood that the oral mucosal cavity's mucosal membrane will facilitate a prolonged delivery.

Buccal adhesive solutions provide a wide range of advantages in terms of accessibility, administration and withdrawal, retentivity, limited enzymatic activity, economy, and high patient compliance. The bioavailability of drugs administered systemically is improved by these drug delivery systems' adhesions to mucosal membranes, which increase the gradient of drug concentration at the site of absorption.

In order to prevent the gastrointestinal side effects of the medicine (when taken orally) and non-invasive injection administration, the study focuses on the development and evaluation of a novel buccal drug delivery strategy for ketorolac.

The bioavailability of oral drugs is now being increased by scientists employing a range of approaches to create buccal adhesive systems. The use of pH modifiers, enzyme inhibitors, and permeability enhancers to change formulation procedures is one of these techniques.

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REFERENCES

1. Shojaei AH. Buccal mucosa as a route for systemic drug delivery: a review. J Pharm Pharmaceutical Sci, 2021; 17(4): 15-30.
2. Radha Bhati, Raja K Nagrajan. A detailed review on oral mucosal drug delivery system. Int J Pharm Sci Res. 2019; 3(3): 659-681.
3. https://en.wikipedia.org/wiki/Buccal_administration (last accessed on May 8, 2022)
4. Gilhotra RM, Ikram M, Srivastava S, Gilhotra N. A clinical perspective on mucoadhesive buccal drug delivery systems. J Biomed Res. 2014;28(2):81–97.
5. Shaikh R, TRR Singh, Garland MJ, Woolfson AD, Donnell RF. Mucoadhesive drug delivery systems. J Pharm Bioallied Sci. 2018; 3(1): 89–100.
6. RoyS, Pal K, Anis A, Pramanik K, Prabhakar B, Polymers in mucoadhesive drug delivery system: a brief note, Des. Monomers Polym. 2019; 3(12): 483–489.
7. Sudhakar Y, Kuotsu K, Bandyopadhyay AK, Buccal bioadhesive drug delivery: a promising option for orally less efficient drugs. J Control Release. 2017; 11(9): 15–40.
8. Lieberman HA, Lachman, Schwartz B. Pharmaceutical Dosage forms: Tablets Volume 1. 2nd ed. New York: Marcel Dekker; 1989.
9. Parth S Patel, Ashish M Parmar, Nilang S Doshi, Hardik V Patel, Raxit R Patel. Buccal drug delivery system: a review. Int J Drug Dev Res. 2013; 5(3): 35-48.
10. Patil SB, Murthy RSR, Mahajan HS, Wagh RD, Gattani SG. Mucoadhesive polymers: means of improving drug delivery. Pharma Times. 2006; 38(4): 25-28.
11. https://www.ncbi.nlm.nih.gov/pubmed/1494990 (last accessed on May 9, 2019)
12. Burak Celik. Risperidone mucoadhesive buccal tablets: formulation design, optimization and evaluation. Drug Des Devel Ther. 2019; 11(3): 3355-3365.
13. Rupinder Kaur, Sukhdev Singh, Aaliya Hasan, Sunny Jalhan, Upendra K Jain. Development and evaluation of UV spectrophotometric method for the estimation of ketorolac tromethamine in bulk drug. World J Pharm Pharm Sci. 2016; 5(4): 1792-1799.
14. Raghavendra N Rao, Shravani B, Mettu Srianth Reddy. Overview on buccal drug delivery systems: J Pharm Sci Res. 2013; 5(4): 80-88.
15. Marwa Shukar, Amal Abdel Reheem. Development and evaluation of ketorolac mucoadhesive buccal tablets; Int J Pharm Pharm Sci. 2014; 6(8): 294- 298.
16. Raja Navamanisubramanian, Raghunandan Nerella, Chamundeeswari Duraipandian, Shanmuganathan Seetharaman. Quality by design approach for optimization of repaglinide buccal tablets using box behnken design. Future Journal of Pharmaceutical Sciences. 2018; 4(2): 265-272.
17. Patel Sweety, Anuradha Patel, Sachin Narkhede. Formulation evaluation and optimization of buccal tablets of ivabradine hydrochloride. J PharmSciBioScientific Res. 2016; 6(3): 329-337.
18. Hardik Parmar, Biswajit Biswal, Jyotiranjan Nayak. Design development and evaluation of buccal tablet containing nicorandil. Asian J Pharm Clin Res. 2015; 8(2): 102- 106.
19. Anna Balaji, Vadepalli, Radhika, Vishnuvardhan Goud.Formulation and evaluation of mucoadhesive buccal tablets by using natural polymer. Int J Pharma Sci Res. 2014; 5(3): 4699- 4708.
20. Nisreen Hasan, Khar RK, Javed Ali. Development and evaluation of buccal bioadhesive tablet of an anti-emetic agent ondansetron. AAPS PharmSciTech 2009; 10(4): 1085-1093.
21. Venkataswamy M, Santhoshini M, Priyanka JP, Prathyusha. Preparation and evaluation of biphasic bilayered buccal tablet containing ketorolac immediate release layer and domperidone maleate sustained release layer. World J Pharm Res. 2018; 7(11): 905-945.
22. Rahamatullah Shaikh, Thakur Raghu Raj Singh, Ryan F Donelly.Mucoadhesive drug delivery systems. J Pharm Bioallied Sci. 2011; 3(1): 89- 100.
23. Perioli L, Ambrogi V, Rubini D, Giovagnoli S, Ricci M, Blasi P, et al. Novel mucoadhesive buccal formulation containing metronidazole for the treatment of periodontal disease. J Control Release. 2004; 95(11):

521-533.
24. Balamurugan Mohan, Saravana VS, Ganesh P, Senthil SP, Hemalatha PV, Sudhir V Pandya.Development and in-vitro evaluation of mucoadhesive buccal tablets of domperidone. Res J Pharm Tech. 2008; 1(4): 377-380.
25. Hiremath JG, Sarfaraz MD, Hiremath D, Sarudkar SA. Preparation and physicochemical characterization of simvastatin loaded mucoadhesive bilayered tablet. Indian Journal of Novel Drug Delivery. 2009; 1(1)**:** 18-24
26. Binu Raina, Abhimanyu Sharma, Prabhjot Singh Bajwa. Formulation, evaluation and optimization of fast disintegrating tablet of ketorolac tromethamine. Int J Pharm Investig. 2017; 48(6): 233-246.
27. Khaleed M Hosny, Ravda Zaki, Ahmed Khamies Mohamed, Ahmed Abdelbary. Preparation, characterization and in vivo evaluation of ketorolac tromethamine in situ ocular hydro gel. Indian J Drug Dev. 2011; 3(3): 315-330.
28. Sinha VR, Kumar RV, Singh G. Ketorolac tromethamine formulation: an overview. Expert Opin Drug Deliv. 2009; 6(9): 961-975.
29. Luana Perioli, Valeria Ambrogi, Stefano Givagnoli, Maurizio Ricci. Mucoadhesive bilayer tablet for buccal sustained release of flurbiprofen. AAPS PharmSciTech. 2007; 8(3): E20-E27.
30. Bytul M Rahman, Mukhlesur M Rahman, Maruf Ahmed, Ranjan K Barman, Robiul Islam. Development, evaluation and formulation of ketorolac tromethamine tablet and a comparative study with marketed products.Res J Medicine Med Sci. 2007; 2(2): 102-105.
31. Anup K Roy, Vinod SM, Syed Jalaluddin Basha, Rabiul Haque, Roopa Kark. Formulation and evaluation of mucoadhesive buccal tablets of valsartan. Int J Drug Dev Res. 2013; 5(4): 145-155.
32. Prasantha Vasantha Viswanadhan, Anand Padole, Abin Abraham, Sam Thomarayil Mathew. Buccal tablets of lisinopril by direct compression method for buccal drug delivery. Int Res J Pharm. 2012; 2(2): 30-38.
33. Gore Meghna Milind, Gurav Yogesh, Adhikrao Yadav. Int J Pharm Sci Res. Formulation and evaluation of mucoadhesive buccal tablets of propanolol using natural polymer. 2017; 6(2): 2905-2913.
34. Goswami Druba Shankar, Goyal Sandeep, Goyal Deepak, Sharma Rini, Mehta Naveen, Puja Kumari, et. al. Formulation and evaluation of mucoadhesive tablets of famotidine. J Pharm Biomed Sci. 2011; 12(6): 279-280.
35. Aswathy V.S, Ganesh Sanker. S, M.A Kuriachan, Formulation and Evaluation of Mucoadhesive Buccal Tablet of Antianginal Drug, Ijppr.Human, 2018; Vol. 13 (1): 43- 71.
36. Burak Çelik, Risperidone mucoadhesive buccal tablets: formulation design, optimization and evaluation, Drug Design, Development and Therapy 2017:1114.
37. Anroop B. Nair, Jigar Shah, Shery Jacob, Bandar E. Al-Dhubiab, Vimal Patel, Nagaraja Sreeharsha, Pottathil Shinu, Development of Mucoadhesive Buccal Film for Rizatriptan: In Vitro and In Vivo Evaluation, Pharmaceutics 2021; 13: 728-735.
38. Mohammad Ali Daneshmehr, Hilda Adibpour, Zahra Ataie, formulation and evaluation of hydrocortisone sodium succinate mucoadhesive buccal tablet, International Journal of Pharmaceutical Investigation, 2020; Vol 10, Issue 3, 273-282.
39. Karen Lu Li and Agnes Llamasares Castillo, Formulation and evaluation of a mucoadhesive buccal tablet of mefenamic acid, Brazilian Journal of Pharmaceutical Sciences, 2020;56: 264-271.