RESEARCH ARTICLE

Formulation Development of Mucoadhesive Tablets for Treatment of Hypertension using Losartan Potassium

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ABSTRACT

Controlled-release losartan potassium incorporated bucccoadhesive tablets were prepared using guar gum and hydroxy propyl methylcellulose K4M (HPMC K4M). The polymers had demonstrated considerable influence for all reactions. Ethylcellulose, a naturally impermeable material, was employed as a backing layer. The direct compression approach was used to create nine distinct losartan potassium formulations. Drug and polymer compatibility was determined through preformulation research utilizing fourier transform infrared (FTIR) spectroscopy. Buccoadhesive tablets were evaluated by swelling, bioadhesive characteristics, pH and *in-vitro* drug dissolution. The bioadhesive strength of guar gum was found to be greater than that of HPMC K4M. The swelling effect provided by both polymers was adequate. All formulations were judged to have an adequate surface pH, with values falling between 7 and 5, suggesting no discomfort to the buccal cavity. *Ex-vivo* residence times ranging from 7.2 to >10 hours for all tablets tested demonstrated a high degree of adhesion. The improved formulation follows Fickian diffusion release process. The optimized formulation underwent a stability investigation in accordance with International Council for Harmonisation (ICH) criteria, and no significant changes were found.

Keywords: Anti-hypertensive, Losartan potassium, Mucoadhesive, Tablet.

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INTRODUCTION

The oral method of medicine delivery is perhaps the most popular choice among patients and doctors.[1] However, there are a few medications for which this approach isn't ideal. Numerous factors, such as GIT-pH conditions, enzymes linked to gastrointestinal tract (GIT) membranes, and GI fluids' enzyme content, might contribute to bioavailability issues. The medication is transported immediately to the liver by the blood that drains the GIT, where it undergoes first-pass metabolism and has a restricted bioavailability. Altering the drug's formulation or administration method might sometimes alleviate issues that are inherent to the drug itself. The systemic administration of medications can be avoided by using the parenteral, mucosal, or transdermal routes instead of the liver's first-pass metabolism.[2-4] If a drug delivery device is mucoadhesive, it can be used to keep drug in touch with the oral mucosa for an extended period of time due to the thin coating of mucin that covers its surface. Because of its close proximity to the absorbing membrane, the system minimises the differential path and maximises the drug concentration gradient across the biological membrane. This suggests that the oral mucosa could serve as a venue for slow or long-term medication release.[5-7]

Since the flow of saliva is less in the buccal and gingival locations compared to the sublingual region, the delivery system will remain adhered to these sites for a longer period of time. Proteins, oligonucleotides, polysaccharides, and conventional tiny pharmacological molecules are all candidates for administration via the buccal route due to their size, hydrophobicity, and inherent instability.[8] Both local and systemic treatment can be administered through the mouth. Oral infections, dental caries, mouth ulcers, and stomatitis are all conditions that can be treated locally.[9] When it comes to protein and peptide administration or the systemic transport of tiny compounds that undergo first-pass metabolism, the buccal route is of particular importance.[10-14]

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The current project aims to create and evaluate a bilayered buccoadhesive tablet that contains losartan potassium in order to achieve unidirectional drug release and increase the medication's bioavailability.

MATERIALS AND METHODS

Materials

A complimentary sample of losartan potassium was received. The gift sample got was hydroxypropyl methyl cellulose K4M (HPMC K4M). Analytical grade chemicals and reagents were utilized for all other experimental procedures.

Compatibility Study

The study aimed to evaluate the compatibility between losartan potassium, a pharmaceutical compound, and two polymers, namely guar gum and HPMC K4M. This assessment was conducted by examining their fourier transform infrared (FTIR) spectra utilizing the KBr disc method. The experimental protocol involved the dispersion of a sample in potassium bromide (KBr) followed by the compression of the mixture into discs using a hydraulic press. This compression process applied a pressure of 5 tons for a duration of 5 minutes. The tablet was positioned within the optical pathway, allowing for the acquisition of a spectrum. This spectral analysis was conducted with the purpose of identifying the various functional groups and bands present within the medication or its mixture.[15,16]

Formulation Development of Tablets

Various grades of polymer were utilized, each with varied concentrations. The specified amounts of drug and polymers were mixed for a duration of 10 minutes. A gradual addition of an appropriate amount of polyvinyl pyrrolidone to isopropyl alcohol was performed in order to obtain a cohesive mass resembling dough. The dough mass was passed through a 20/35 mesh screen and thereafter subjected to drying at a temperature range of 55 to 60°C for a specific duration until the loss on drying reached 2%. The granules were gathered and stored in hermetically sealed containers packed with two layers of polyethylene. The granules underwent compression utilizing 6 mm flat round punches.[17-19] The ethyl cellulose backing layer was applied to one side of the crushed tablet, as indicated in Table 1.

Preliminary Compression Analysis

The evaluation of pre-compression properties included the angle of repose, bulk density, tapped density, Hausner's ratio, and Carr's compressibility index.

Buccoadhesive Tablet Evaluation

Hardness, thickness, friability, weight variation and drug content were evaluated for prepared buccoadhesive tablets.

pH studies

The tablets were left at room temperature for two hours in 1-mL of distilled water, and the electrode was used to measure the pH by contacting the tablet's surface and letting it stabilize for one minute.[20,21]

Table 1: Losartan potassium buccoadhesive tablet composition

Ingredients (mg)	*B1*	*B2*	*B3*	*B4*	*B5*
Losartan Potassium	20	20	20	20	20
HPMC K4M	30	30	30	30	30
Guar Gum	-	-	-	-	-
Lactose	30	30	20	25	25
Aerosil	5	0	5	2	0
Ethyl cellulose	15	20	25	23	25

Ex-vivo mucoadhesive study

A piece of buccal mucosa membrane was attached to the surface of the glass slide using a rubber band. Using double adhesive tape buccoadhesive tablet was attached to the bottom of beaker. The tablets were in contact with the mucosa for 2 minutes while being applied with a constant force of 5 grams. Specimens are maintained in a "Krebs-Henseleit buffer solution." To encourage direct contact between the tissues and tablet, two minutes of contact time were allotted. The tablet was then submerged in water delivered by pipette until it was no longer adhered to the buccal mucosal membrane. To determine mucoadhesive strength, we applied a force (in grams) to a tablet pressed on a membrane.[22-24]

Swelling index

The investigation focused on the swelling characteristics of all formulations. Buccoadhesive tablet was placed in Petri dish filled with phosphate buffer pH 6.8. The temperature of the solutions was maintained at 37 ± 0.5°C. At regular time intervals, the tablets were removed from the petri dish. The tablets were subjected to a desiccation process using filter paper in order to eliminate any residual moisture, after which their weight was measured. The mass of the expanded tablet was determined. The swelling index was calculated using the equation provided.[25-27]

$$\text{Swelling Index} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} * 100$$

In-vitro release study

The purpose of this study was to employ the USP type II dissolution test apparatus to calculate the buccal tablet release rate *in-vitro*. Medicine in tablets is often released from just one side. This was accomplished by coating one side of the tablet with an impermeable backing membrane. The tablets were then glued to a 2 by 2 cm glass slide with cyanoacrylate glue and placed in a solvent for dissolution. A 500 mL phosphate buffer solution with a pH of 6.8, 50 revolutions per minute, and 37 ± 0.5°C was used for the dissolving test. The samples were taken over a period of up to eight hours at different intervals. They were examined in a UV-visible spectrophotometer at a maximum absorption wavelength of 250 nm following the appropriate dilution.[28, 29]

Ex-vivo permeation study

Extracted buccal mucosa from sheep was used in an experiment to assess the *ex-vivo* penetration of losartan potassium from

a buccoadhesive tablet. A Franz diffusion cell was used to examine permeation at a temperature of 37 ± 2°C. Sheep with less than 2 hours between their killing and use had their buccal mucosa samples collected and used. Following collection, the tissue was kept in a phosphate buffer solution with a pH of 6.8 and maintained at a temperature of 4°C. Isolated sheep buccal mucosa was placed into a diffusion cell with the mucosal smooth side facing the donor chamber. The buccal tablet was selected for the experiment, it was applied to the mucosa, and the compartments were shut. One mL of phosphate buffer solution at a pH of 6.8 was put into the donor compartment. The receptor compartment was filled with a solution of 6.8 pH phosphate buffer. Swirling at 50 rpm with a magnetic bead stabilized the hydrodynamics of the receptor compartment. The diffusion process took eight hours to finish. One mL of the solution was removed and replaced with the same volume of 6.8 pH phosphate buffer at each time point. Spectrophotometric examination at a wavelength of 250 nm was performed on the filtered aliquots using a UV-visible spectrophotometer.[30,31]

Stability Analysis

Stability studies were done in compliance with the International Council for Harmonization (ICH) principles. Following three months at 40°C and 75% relative humidity in a humidity room, the aluminum-sealed optimised buccal tablets were stored. The samples were periodically analysed to assess drug concentration, release, surface pH and other physicochemical properties.[32]

RESULTS AND DISCUSSION

Compatibility Study

In order to examine the compatibility between the drug and excipient, as well as between the excipients themselves, the FTIR spectra of the drug and excipients were merged at a 1:1 ratio. FTIR research confirmed losartan potassium's presence in the formulation. Pure potassium losartan has distinct peaks in its infrared absorption spectra at certain wavenumbers. One of these peaks is an absorption at 3190.97 cm^{-1}, which is in line with C-H bond stretching. C-H stretching is also linked to a second peak at 2953.79 cm^{-1}. Additionally, a peak is seen at 1459.20 cm^{-1}, which is indicative of C-H bond distortion in methyl groups. Finally, the stretching of C=C bonds is represented by a peak at 1621.77 cm^{-1}. There appears to be no chemical interaction between losartan potassium and the polymers because these peaks are present in both the pure drug and formulation B5. The infrared (IR) spectrum analysis suggested that no significant interaction between the drug and the excipients was detected (Figure 1).[26-31]

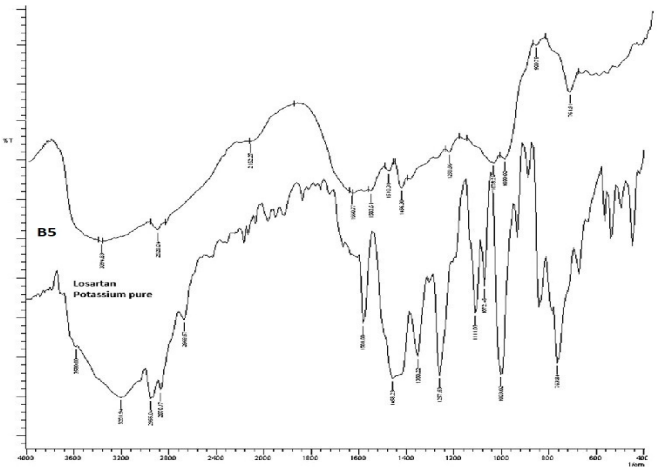

Figure 1: FTIR spectrum of losartan and B5

Pre-compression Study

Table 2 displays the outcomes of the pre-compression parameters. The bulk density and tapped density measurements were observed to fall within acceptable limits, suggesting that the packaging qualities necessary for compression are satisfactory across all formulations. The compressibility index of Carr was determined to be within an acceptable range, suggesting favorable compressibility. The angle of repose and Hausner's ratio were observed to be within acceptable limits, indicating favorable flow characteristics.

Post-compression Study

Since guar gum and HPMC K4M, two mucoadhesive polymers, have desirable traits such a high-water absorption capacity, the ability to stick to the oral mucosa, and delayed medicine release capabilities, they were incorporated into the formulation of buccoadhesive tablets. Table 3 summarizes the outcomes relevant to the physical properties of the losartan potassium tablets. It was determined that the buccoadhesive tablets fell within a satisfactory range of uniformity with regards to both weight and thickness. The tablets' hardness ranged from 5.5 ± 0.40 to 5.8 ± 0.12 kg, while their thickness varied from 2.73 ± 0.004 to 2.75 ± 0.008 cm. The hardness of the bioadhesive tablets demonstrated variation based on the exact type and percentage of the bioadhesive polymers applied. Regardless of tablet hardness, there was no change in the drug release from the hydrophilic matrices. The drug release process, which necessitates diffusion through the gel layer and degradation of this layer, is unaffected by the tablet's dryness. Drug content of tablets was found to be in range of 97.55 ± 0.45 to 98.98 ± 0.64%. Saliva can have a pH between 5.6 to 7.0, and the surface pH values of formulations B1 to B5 ranged from 6.34 to 6.65, therefore they are well within that range. Thus, it was concluded that no formulation was capable of producing mucosal surface irritation at the local level.

Ex-vivo mucoadhesive study

Researchers found that the more mucoadhesive polymer there was, the stronger the adherence. Buccal tablets made with Guar gum had better mucoadhesion than those made using HPMC K4M as the mucoadhesive polymers. Tablets with HPMC K4M as the mucoadhesive polymer were shown to have a mucoadhesion strength of B5 > B4 > B3 > B2 (Figure 2).

Swelling index

Mucoadhesive polymer HPMC K4M and guar gum tablets gradually expanded throughout testing, and the expanded tablets retained their structural integrity for up to 6 hours.

Table 2: Pre-compression study

Batch	*Angle of repose (°)*	*Bulk density (g/mL)*	*Tapped density (g/mL)*	*Compressibility index*	*Hausner's ratio*
1	31.2 ± 0.21	0.325 ± 0.02	0.345 ± 0.02	13.33 ± 2.007	2.66 ± 0.058
2	32.3 ± 0.82	0.364 ± 0.02	0.398 ± 0.02	13.45 ± 0.324	2.54 ± 0.033
3	32.1 ± 1.68	0.124 ± 0.03	0.365 ± 0.02	15.82 ± 2.657	2.65 ± 0.045
4	31.3 ± 0.58	0.247 ± 0.02	0.354 ± 0.01	17.54 ± 2.367	2.35 ± 0.050
5	31.8 ± 0.47	0.234 ± 0.02	0.321 ± 0.02	17.31 ± 3.657	2.33 ± 0.098

Table 3: Post-compression study

Batch	*Thickness (cm)*	*Hardness (kg)*	*Friability (%)*	*Average weight variation (mg)*	*Drug content (%)*	*Surface pH*
B1	3.89 ± 0.02	4.6 ± 0.51	0.578	100.31 ± 2.43	97.77 ± 0.66	5.44 ± 0.01
B2	3.85 ± 0.02	6.8 ± 0.32	0.547	101.40 ± 2.31	98.98 ± 0.64	5.35 ± 0.02
B3	3.84 ± 0.05	5.3 ± 0.64	0.568	101.01 ± 2.20	97.55 ± 0.45	5.41 ± 0.02
B4	3.82 ± 0.06	6.4 ± 0.55	0.569	100.74 ± 2.66	97.65 ± 0.63	5.60 ± 0.02
B5	3.81 ± 0.03	5.2 ± 0.65	0.574	100.32 ± 2.32	98.33 ± 0.99	5.50 ± 0.02

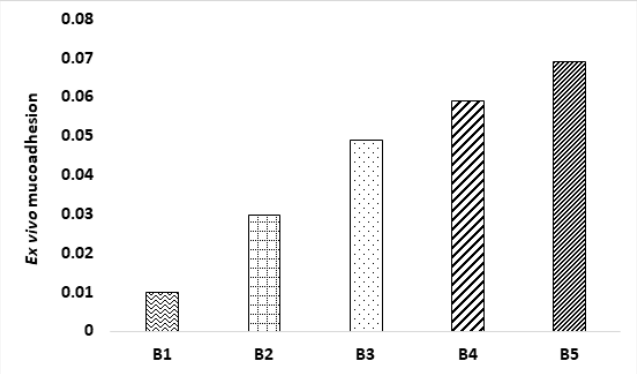

Figure 2: *Ex-vivo* mucoadhesive study

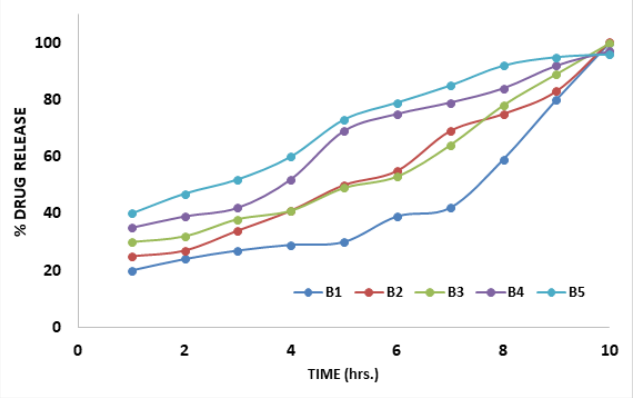

Figure 3: Relative dissolution profiles of formulations

Over the course of 1 to 6 hours, the swelling index of tablets containing HPMC K4M as a mucoadhesive polymer increased. Additionally, it was noticed that an increase in the polymer content resulted in an increase in the swelling index of the tablet formulations incorporating HPMC K4M. It was found that B5 swells more than B4 and B3 and B2 combined. With guar gum serving as the matrix carrier, the swelling index of the tablets went from 1 to 6 hours. Based on the findings, the tablet formulations' swelling index rises with an increase in polymer content. Greater swelling characteristics was revealed by the formulation that included guar gum as the mucoadhesive polymer. One way ANOVA determined to be significant at all times.

In-vitro release studies

The drug release percentage from B1 was determined to be 99.95%. The formulations B2, B3, B4, and B5 were produced utilizing varying weight percentages of HPMC K4M as the polymer, specifically 25, 30, 35, and 40% w/w. During a 6-hour test period, it was shown that formulations B2, B3, B4, and B5 released 100.30, 99.79, 97.07, and 95.97% of the medication, respectively. Slope values suggest that drug release slows steadily as HPMC K4M content increases as a proportion of total weight. Rankings were obtained for B2, B3, B4, and B5 in that order (Figure 3). The slope values show a negative association between guar gum percentage and medication release rate, suggesting that the release rate gradually decreases with increasing guar gum percentage. One-way analysis of variance (ANOVA) was used to do statistical analysis on the data. The information available at any moment has been found to be valuable.

Ex-vivo permeation study

The experiment on permeation *ex-vivo* lasted for 8 hours. The measured flow of B1 was determined to be 0.691 µg/cm^2/h (Table 4). B2, B3, B4, and B5 flow values were calculated. *Ex-vivo* measurements show a slope consistent with the medication being able to pass the membrane, although at a slow rate (Figure 4). The mucosa serves as an obstruction to drug transport, which explains why this is the case. The observed slope linearity was found to be quite high. The researchers found that the rate of release slowed down as the polymer concentration in the tablet increased. One-way analysis of variance (ANOVA) was used to do a statistical analysis on the data. The information available at any time has been found to be important.

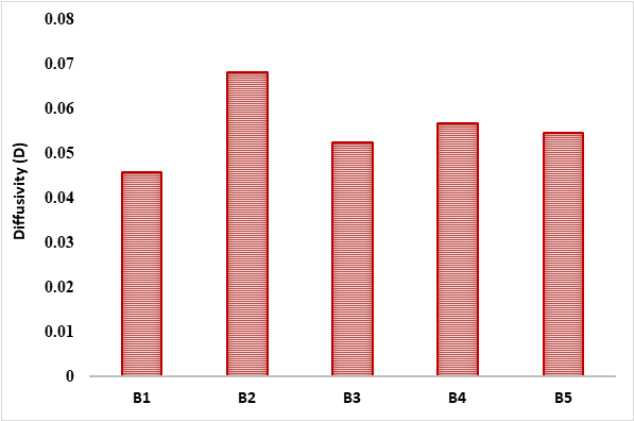

Figure 4: Diffusivity of formulations

Table 4: *Ex-vivo* permeation study

Sr. No.	*Batch*	*Diffusivity (D)*	*Flux (Jss)*
1.	B1	0.0457	0.789
2.	B2	0.0681	0.798
3.	B3	0.0523	0.778
4.	B4	0.0567	0.765
5.	B5	0.0544	0.724

Accelerated stability

Buccoadhesive tablets were tested for stability by placing them in aluminum foil and subjecting them to 40°C and 75% relative humidity. Stability tests were performed on formulation B5, and the results showed no significant changes. One-way analysis of variance (ANOVA) was used to do statistical analysis on the data. The information available at any time has been found to be important.

CONCLUSION

In the current investigation, wet granulation was used to create losartan potassium buccoadhesive tablets using guar gum and HPMC K4M as active excipients. FTIR investigations suggested that no major interactions existed between the drug and polymer, or between the various polymer components. This quality is essential for keeping the formulation's structural integrity while yet ensuring its bioadhesive characteristics. An increase in polymer concentration has a considerable effect on the swelling index. The buccal tablets performed well in mucoadhesive tests, with mucoadhesion increasing in direct proportion to polymer concentration. The buccal tablets containing guar gum displayed enhanced mucoadhesive qualities. An investigation on the *ex-vivo* permeation of losartan potassium revealed that the tablets had greater flux and permeability. The choice to investigate formulation F5's stability was influenced by investigations on swelling index and mucoadhesive strength. According to analyses of the release kinetics of the batches, the Peppas and zero-order models suit the data the best. Twenty-one days of stability testing at 40°C and 75% relative humidity were performed on tablets from batch B5. The formulation of the tablets was found to be stable after an evaluation of the drug content and drug release.

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