FORMULATION AND EVALUATION OF MUCO-ADHESIVE BUCCAL PATCHES OF ALISKIREN USING OKRA GUM

Hina Sharma[1], Tapasvi Gupta[1], Nitish Gaur[2], Seema[3],

Jatin Kumar[4], Khushal Garg[5],

[1]Gyan vihar school of pharmacy, Suresh Gyan vihar University Jaipur
[2]Mangalayatan University Aligarh
[3]Mahatma Gandhi Institute of Pharmacy, Lucknow
[4]Rama & Krishna College of Pharmacy

Corresponding author: Corresponding author: tapasvi.gupta@mygyanvihar.com

Abstract

Aliskiren is a direct renin inhibitor used to treat high blood pressure by relaxing blood vessels, allowing the heart to pump blood more efficiently. Traditional rapid-release doses necessitate frequent administration due to quick declines in therapeutic levels. To address this, researchers developed controlled-release mucoadhesive buccal patches designed to release Aliskiren slowly over eight hours, maintaining therapeutic levels and reducing dosing frequency. The patches were formulated using okra gum, hydroxyethyl cellulose (HEC), polyvinyl alcohol (PVA), and polyvinylpyrrolidone (PVP) as matrix-forming agents, with propylene glycol as a plasticizer. Stability was confirmed using Fourier transform infrared spectroscopy (FTIR). Patches were prepared via a solvent casting method and evaluated for quality and effectiveness, including tests for thickness, folding endurance, weight variation, water uptake, bioadhesive strength, mechanical strength, surface pH, and drug release properties. Among various formulations, formulation F3 exhibited optimal performance, showing strong bioadhesive strength, controlled drug release, and favorable results across all parameters, maintaining drug release over eight hours. Drug release mechanisms were analyzed using Zero order, First order, Higuchi matrix, and Peppas model equations, with all formulations fitting best into the Peppas model, indicating a combination of diffusion and erosion mechanisms (n values between 0.6 and 0.9). This study demonstrates a significant advancement in drug delivery for high blood pressure treatment through the development of controlled-release mucoadhesive buccal patches, enhancing drug efficacy and patient compliance. The success of formulation F3 underscores the potential for applying similar methodologies to other medications**.**

Keywords: - Aliskiren, High blood pressure, Direct renin inhibitor, Okra gum, Solvent casting method.

1. Introduction

The development and testing of mucoadhesive buccal patches of Aliskiren, produced from okra gum, has marked a significant advancement in drug delivery technology. This innovative technique utilizes the unique properties of okra gum, a naturally occurring polymer derived from Abelmoschus esculentus, commonly known as ladyfinger or okra. Treatment for hypertension and related cardiovascular conditions may involve the use of renin inhibitors like alisikren(1). However, problems with conventional oral delivery include systemic side effects and unequal absorption. The mucoadhesive buccal patch technology aims to address these shortcomings by providing the potential for both regulated and sustained medication release and localized therapeutic benefits. We chose okra gum as a mucoadhesive polymer due to its biodegradability, biocompatibility, and mucoadhesive properties. The buccal patches' mucosal adhesion allows for prolonged interaction with the mouth mucosa, improving medication absorption and bioavailability(2). The unusual combination of okra gum and aliskiren in buccal patches is a wonderful example of how the natural and medical sciences come together. To achieve the desired drug release profile, the study thoroughly investigates the optimal ratios of okra gum to aliskiren. Additionally, the study employs a variety of manufacturing and characterization methods for patches to ensure product quality, uniformity, and adherence to pharmaceutical criteria. The comprehensive review includes studies on physicochemical properties, compatibility assessments, mucoadhesion strength, and in vitro drug release kinetics. Additionally, the study emphasises the therapeutic advantages of buccal medicine distribution, including improved patient compliance, fewer gastrointestinal adverse effects, and higher drug stability. Mucoadhesive buccal patches that gradually release Aliskiren may enhance treatment outcomes and increase patient comfort(3). In conclusion, the development and evaluation of Okra gum-based mucoadhesive buccal patches of Aliskiren represent a groundbreaking endeavour at the intersection of the natural and pharmaceutical sciences. This

study aims to provide informative information on developing efficient and patient-friendly drug delivery systems, which may have implications for the pharmaceutical research and development community(2).

Orally or by mouth are the most popular and practical ways to administer medication. Because it offers greater design flexibility than alternative delivery systems, it has piqued a lot of interest in the pharmaceutical industry. It's simple to administer, and since people eat meals every day, it's widely known that oral medications are well absorbed. Most oral drugs are immediate-release varieties, which release the substance quickly to encourage speedy absorption. "Drug delivery" encompasses a wide range of techniques used to administer medication to the human body. Even though oral administration is becoming more common, there are drawbacks to more conventional approaches like needles and pills. Because the hepatic system is involved, tablets may not release the desired amount of drug into the bloodstream(4). Furthermore, many soluble tablet medications cause liver damage, which is a terrible adverse effect. To get over these restrictions, scientists and researchers are investigating a variety of medication delivery strategies. Researchers have developed and tested mucoadhesive buccal patches of Aliskiren, a significant breakthrough in drug delivery technology. This inventive method makes use of the special qualities of okra gum, a naturally occurring polymer generated from Abelmoschus esculentus, popularly known as ladyfinger or okra. Cardiovascular diseases such as hypertension can benefit from the use of renin inhibitors like alisikren. However, there are issues with uneven absorption and systemic adverse effects. Mucoadhesive buccal patch technology can address these issues by enabling targeted therapeutic benefits and controlled, long-lasting drug release(5). Okra gum's mucoadhesive, biodegradable, and biocompatible qualities led to its selection as a mucoadhesive polymer. The buccal patches' mucosal adherence facilitates a longer interaction with the oral mucosa, which improves drug absorption and bioavailability. The peculiar pairing of aliskiren and okra gum in buccal patches is a fantastic

illustration of the integration of the natural and medicinal sciences. The study carefully examines the ideal ratios of okra gum to aliskiren to obtain the intended medication release profile. Furthermore, the study employs a variety of production and characterization techniques for patches to ensure product excellence, consistency, and compliance with pharmaceutical standards(5). The in-depth analysis includes tests on the physicochemical properties, compatibility, mucoadhesion strength, and the rate at which the drug is released in vitro. The study also highlights the therapeutic benefits of buccal medicine delivery, such as increased drug stability, fewer gastrointestinal side effects, and better patient compliance. Mucoadhesive buccal patches that progressively release Aliskiren may improve treatment outcomes and boost patient comfort. In conclusion, the creation and assessment of Aliskiren's Okra gum-based mucoadhesive buccal patches represent a revolutionary initiative at the nexus of pharmaceutical and natural sciences. The purpose of this study is to provide useful information on creating effective and patient-friendly medication delivery systems(6). This research's findings may have implications for the entire pharmaceutical research and development community.

Other methods of medication distribution into the body were looked into to overcome some of these restrictions. Those are

1. Transdermal Drug Delivery System (via skin that is still intact)

2. Trans Mucosal Drug Delivery Systems (by the nose, mouth, intestine, rectum, or vaginal mucosa that is still intact)

3. Drug Delivery System Trans Ocular (through the eye)

4. Inhaling through the lung tissue using the Trans Alveolar Drug Delivery System

5. Implantable Drug Delivery System (transport into surrounding tissue through deeper and subcutaneous implants)

6. Injectables (subcutaneous or I.M.).

Among the aforementioned modes, there has been varied commercial adoption for transdermal, transmucosal, injectables, and subcutaneous implants(7).

TRANSMUCOSAL DRUG DELIVEY SYSTEM

One of the absorbent mucosa's primary benefits is its capacity to transport medication to easily accessible bodily areas such as the mouth, eyes, nose, rectum, and vagina. This approach eliminates the need for the early clearance of the liver and gastrointestinal tract that occurs with oral delivery. Furthermore, because of the distinct chemical and physical characteristics of these mucosal membranes, certain types of medicines—such as those that prefer or reject water—can be absorbed more readily(8).

Various types of transmucosal drug delivery systems are

- Buccal Drug Delivery System.
- Ocular Drug Delivery System.
- Vaginal Drug Delivery System.
- Rectal Drug Delivery System.
- Nasal Drug Delivery System.
- Gastro Intestinal Drug Delivery System

BUCCAL DRUG DELIVERY SYSTEM

The oral mucosa and skin are more comparable in structure than other parts of the gastrointestinal tract. Because of its higher permeability, the oral mucosa in the mouth is less effective at absorption than the colon(9). This is because the stratified epithelium, the outermost layer of the mouth's cells, differs in maturity from the bottom layer to the surface. For a long time, people have applied drugs topically to the oral mucosa, but there is a growing interest in

directly delivering medications into the bloodstream through the mouth. This method has a number of benefits despite its relatively low permeability, such as the capacity to administer medications without requiring the liver to first break them down, simple access to the delivery site, and the possibility of continuous drug release, particularly through the cheek tissues. If necessary, the oral route also allows for prompt cessation of medication delivery. Drug delivery via the oral mucosa is not without its difficulties, though. Improving permeability and ensuring the medication stays where applied are two critical issues. Due to the possibility of removing a substantial portion of the medication from the applied form, frequent saliva production and swallowing may result in low efficacy(10).

Advantages

- There is an abundance of blood flow to the mouth mucosa. After passing through the mouth mucosa, drugs are absorbed from the oral cavity and enter the systemic circulation through the deep lingual or face vein, braciocephalic vein, and internal jugular vein. The medication reaches the systemic circulation directly and avoids the first pass impact by being administered buccal.
- Its high vascularization makes it easier to remove and give dose forms.
- No first-pass hepatic impact occurred.
- There is no gastrointestinal tract pre-systemic metabolism.
- Simplicity of use
- Easy access for patients.
- A region with smooth muscle and mucosa that is largely immobile that is appropriate for the administration of retentive dose forms(11).
- Avert the medications' contact with the digestive juices.

- Faster cellular recuperation and the establishment of a confined area on the buccal mucosa's smooth surface.
- Suitability for medications and excipients that cause moderate, reversible mucosal damage or irritation due to low enzyme activity. A wide variety of foreign substances are frequently introduced to the oral mucosa. Because of this, the membrane has developed into one that is more resilient to harm from drugs, dosage forms, or additives.
- Drug administration by a non-invasive technique.
- Possibility of adding an enzyme inhibitor, pH modifier, or permeability enhancer to the formulation(5).

Disadvantages

- The buccal membrane has less permeability than the sublingual membrane in particular.
- Compact surface (170 cm2).
- The oral cavity continuously secretes 0.5–2 L of saliva each day, which dilutes medications at the site of absorption and causes low drug concentrations at the surface of the absorbing membrane.
- Patient inconvenience when consuming food or liquids(12).

Restrictions on buccal absorption

- The area of absorptive membrane is relatively smaller.
- This method cannot be used to give medications that become unstable at buccal pH.
- Only medications that require a tiny dosage can be given.
- This method of administration is limited to medications that are absorbed through passive diffusion.
- Drinking and eating could be regulated.

- The risk of the patient ingesting the medication never goes away.
- Overhydration can cause a slick surface to form, and the swelling and hydration of the buccoadhesive polymers can compromise the formulation's structural integrity(13).

2. DRUG PROFILE

ALISKIREN

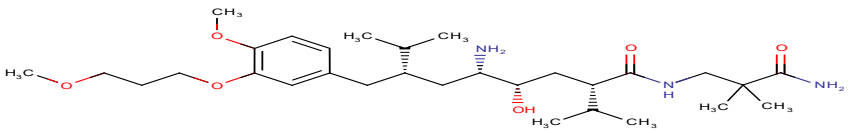
Generic Name

Aliskiren

Description:

Aliskiren is the first medication in the renin inhibitor medicine category and is prescribed for the management of hypertension. The drug was developed jointly by Speedel and Novartis and received first approval from the FDA in early 2007. Aliskiren has been demonstrated to be effective in lowering blood pressure when used alone or in combination with other antihypertensive medications.

Structure:



Molecular formula:

$C_{30}H_{53}N_3O_6$

Chemical name:

(2S, 4S, 5S, 7S)- 5-amino -N -(2 -carbamoyl -2-methylpropyl)-4 -hydroxy -2 isopropyl -7-[4- methoxy-3-(3-methoxypropoxy) benzyl]-8-methylnonanamide.

Melting point:

98-99 °C

Molecular weight:

551.7583

Solubility:

The rate of solubility of aliskiren (hemifumarate) in ethanol, DMSO, and water is around 100 mg/ml. It is not advisable to store the aqueous solution for more than 24 hours. Aliskiren is a renin inhibitor that does not contain peptides. It has a high potency for the human enzyme, with an IC50 value of 0.6 nM.

Therapeutic class:

Aliskiren is a direct renin inhibitor used to manage hypertension.

Pharmacokinetic parameters

Absorption:

Aliskiren is taken up by the gastrointestinal tract and has a low absorption rate, resulting in a bioavailability ranging from 2.0% to 2.5%. The highest levels of aliskiren in the bloodstream are reached within 1 to 3 hours after it is given. Aliskiren reaches steady-state concentrations after 7-8 days of regular treatment.

Distribution:

Unchanged aliskiren accounts for about 80 of the found in plasma.

Metabolism:

Approximately 80% of the medication remains unaltered in the bloodstream after being taken orally. Approximately 1-3% of aliskiren in the plasma can be attributed to two significant metabolites. One of the metabolites is an alcohol derivative that has undergone O-demethylation, whereas the other metabolite is a derivative of carboxylic acid. Plasma may contain small amounts of metabolites that have undergone oxidation and hydrolysis.

Elimination:

Renal route.

Duration of action:

Plasm half-life for aliskiren can range from 30 to 40 hours with an accumulation half-life of about 24 hours.

Mechanism of action/effect:

Aliskiren functions as a renin inhibitor. The kidneys release renin in response to a decrease in blood volume and renal perfusion. Typically, it cuts the angiotensinogen protein to create angiotensin I. Angiotensin I is subsequently transformed into angiotensin II, which is a biologically active protein. Angiotensin II is a powerful agent that constricts blood vessels and stimulates the release of catecholamines into the bloodstream. Furthermore, it stimulates the production of aldosterone, which, along with salt reabsorption, leads to an elevation in blood pressure. In addition, angiotensin II exerts its effects on the adrenal cortex, specifically via promoting the secretion of aldosterone. Aldosterone enhances the reabsorption of sodium and the excretion of potassium in the nephron.
Aliskiren inhibits the process described above by to renin at its active site, so preventing the cleavage of angiotensin and hence inhibiting the production of angiotensin I. This marks the conclusion of the series of angiotensin II mediated processes that typically elevate blood pressure.

Side/adverse effects:

- diarrhea
- stomach pain
- heartburn
- cough
- rash
- dizziness
- headache
- back pain

3. RESEARCH OBJECTIVE

The transmucosal route of medication delivery offers greater advantages than oral administration for achieving systemic drug delivery. Oral mucosal drug delivery is a method specifically intended to administer a sufficient amount of medication through the mucosal surface of a patient. This approach offers several benefits:

• Better bioavailability

• Bypassing first-pass metabolism.

• Avoidance of presystemic elimination of drug in GIT.

• Reduction of side effects.

• To produce controlled release of drug.

• Localization of drug to oral cavity.

• An ideal route of administration of drug for pregnant ladies and post operative vomiting.

Aliskiren is the inaugural medication in the renin inhibitor pharmacological category and is prescribed for the management of hypertension. The drug was jointly developed by Speedel and Novartis and received first approval from the FDA in early 2007. Aliskiren has been demonstrated to be effective in lowering blood pressure when used alone or in combination with other antihypertensive medications.

Aliskiren possesses physicochemical qualities such as low lipophilicity at small doses, stability at the pH of the buccal cavity, lack of taste and odour, and enhanced absorption through the buccal mucosa. These characteristics make it an excellent choice for administration via the buccal route. Therefore, this study aims to develop a buccal mucoadhesive dosage form for Aliskerin in the form of buccal patches using four different polymers: Okra Gum, Hydroxy Ethyl Cellulose (HEC), Poly Vinyl Alcohol (PVA), and Poly Vinyl Pyrrolidone (PVP). The objective is to overcome the issues of hepatic metabolism and low bioavailability.

4. Material and Methods

1. Preformulation studies

- Solubility determination
- Melting point determination.
- Compatibility studies between Aliskerin and polymers used.

2. Preparation of standard curve for Aliskerin.

3. Formulation of buccal patches of Aliskerin using different polymers in different concentrations.

4. Evaluation of Mucoadhesive buccal patches for following parameters

a) Physical parameters

I. Thickness

II. Folding endurance

III. Measurement of surface PH

IV. Water uptake study

b) Performance parameters

I. Drug content uniformity

II. Measurement of bioadhesive strength

III. Mechanical strength

IV. Scanning electron microscopy (SEM)

V. In-vitro release study

VI. Invitro residence time

VII. Ex-vivo drug release study

VIII. Stability study

IX. Kinetic study

The results are presented in tables and graphically by various equations governing release kinetics.

PREFORMULATION STUDIES:

Preformulation testing is the initial stage in the development of medication dosage forms. Pharmaceutical characterization involves studying the physical and chemical properties of a therapeutic component both on its own and when mixed with other substances called excipients. The primary objective of preformulation testing is to gather pertinent data that can assist the formulator in creating dosage forms that are both stable and readily absorbed by the body.

The goals of the Preformulation studies are:

• To establish the necessary physicochemical properties of a new drug substance.

• To determine its kinetic release profile.

• To establish its compatibility with different excipients.

Hence, Preformulation studies on the obtained sample of drug include physical tests and Compatibility studies.

A. Identification tests:

- **IR spectroscopy:** A comparison was made between the IR spectrum of the drug sample obtained and the IR spectra of the pure drug.
- **Solubility analysis:** A solubility analysis was conducted to choose an appropriate solvent system for dissolving the medicine and to assess its solubility in the dissolution media that would be utilised.
- **Melting point determination:** Melting point of drug sample was determined by capillary tube method.

B. Compatibility studies of Aliskerin and polymers:

FT-IR spectra of the drug and a physical combination of the drug with polymers were obtained. The samples were combined with KBr and the spectra was acquired by scanning across the wave number range of 4000-400cm-1. Infrared spectroscopy (IR) is utilised to verify the identity of the drug and identify any interactions betw een the drug and the excipients.

C. Calibration curve.

A. Scanning of drug:

Precisely measured 100mg of Aliskerin and dissolved it in 10ml of methanol, then adjusted the volume to 100ml with pure water. Extract one millilitre from the aforementioned solution and dilute it with distilled water to achieve a final volume of 100 millilitres, resulting in a concentration of 10 micrograms per millilitre. The UV spectrophotometer was used to scan the absorption maxima of the standard solution mentioned above within the wavelength range of 200-400nm, with the blank serving as a reference. The absorption peaks were determined to occur at a wavelength of 229nm.

B. Preparation of calibration curve of Aliskerin

Aliquots of 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10 mL were taken from the standard solution mentioned above. Each aliquot was then diluted with distilled water to a final volume of 10 mL. This process was done to get concentrations ranging from 1 to 10 mcg/mL. The absorbances of these solutions were measured at a wavelength of 229nm, using a blank as a reference.

PREPARATION OF BUCCAL PATCHES:

Patches containing Aliskerin and Okra Gum, HEC, PVP, PVA in varying amounts were made using the solvent casting process. The medication was dissolved in 5ml of methanol, while the polymers were dissolved in a separate container with 20ml of distilled water. The dissolution process for both substances involved constant stirring for a duration of 4 hours. After agitating, combine the medication and polymer solution. Propylene glycol was introduced into the solution as a plasticizer while maintaining continuous agitation. The solution with high viscosity was allowed to stand overnight to assure the formation of a transparent and free from bubbles solution. The solution was transferred into a glass petri dish and left to evaporate at a temperature of 400°C until it solidified into a pliable film. The dried patch was meticulously removed, thoroughly inspected for any flaws or air bubbles, and then cut into pieces with an area of 1mm2. The patches were enclosed in aluminium foil and kept in desiccators to preserve their integrity and flexibility. Table 3 displays the makeup of various buccal patches.

Table no. 3: composition of buccal patches of Aliskerin.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Aliskerin	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg	100 Mg	100 mg
Okra Gum	100 mg	-----	100 mg	100 mg	100 mg	100 mg	------	100 mg	100 mg	100 mg
HEC	-----	750 mg	500 mg	375 mg	250 mg	-----	750 mg	500 mg	375 mg	250 mg
PVP	125 mg	125 mg	125 mg	125 mg	125 mg	------	-----	------	------	------
PVA	------	------	------	------	------	125 mg	125 mg	125 mg	125 mg	125 mg
ETHANOL	5ml	5ml	5ml	5ml	5ml	5ml	5ml	5ml	5ml	5ml
Propylene glycol	0.7 ml	0.7 ml	0.7 ml	0.7 ml	0.7 ml	0.7 ml	0.7 ml	0.7 ml	0.7 ml	0.7 ml
Distilled water	25 ml	25 ml	25 ml	25 ml	25 ml	25 ml	25 ml	25 ml	25 ml	25 ml

EVALUATION OF MUCCOADHESIVE BUCCAL PATCHES OF ALISKERIN

- **Physical parameters**

I. Thickness
II. Folding endurance
III. Measurement of surface PH
IV. Water uptake study

- **Performance parameters**

I. Drug content uniformity
II. Measurement of bioadhesive strength
III. Mechanical strength
IV. Scanning electron microscopy (SEM)
V. In-vitro release study
VI. Invitro residence time
VII. Ex-vivo drug release study
VIII. Stability study
IX. Kinetic study

A. PHYSICAL PARAMETERS:

a) Thickness of patch:

The thickness of the patch was measured at five randomly selected points using a scre w gauge. The mean and standard deviation were computed.

b) Folding endurance:

The folding endurance of the buccal patches was assessed by repetitively folding a 20 mm diameter patch at the same location until it fractured. The folding endurance is determined by the number of times a patch can be folded at the same location withou t breaking. The test was conducted three times and computed the mean and standard deviation.

c) Mechanical strength:

A motorised test stand and cell were part of a microprocessor-controlled force gauge used to evaluate the mechanical characteristics of patches. A 60 x 10 mm patch free of any obvious defects was cut and sandwiched between two clamps spaced 3 cm apart. When the patch was being tested, the clamps were meant to hold it in place without damaging it. Pulling the strips apart until the patch finally broke, the upper clamp moved at a pace of 2 mm/sec while the bottom clamp stayed still. Measured and recorded were the force and the film's elongation at

the time of patch failure. Tensile strength and break elongation were computed using the formula.

WATER UPTAKE STUDY

In addition to determining whether or not the formulations maintain their structural integrity after collecting moisture, the moisture uptake investigations offer valuable insight into the relative moisture absorption capabilities of various polymers. Under the conditions of the experiment, agar was dissolved in hot water at a concentration of five percent by weight or volume. Following the placement of the substance in petri plates, it was allowed to harden. After selecting and weighing six patches from each formulation, we determined that none of them contained any medicines. Before beginning the research, the specimens were first treated with a vacuum oven for a whole night in order to remove any moisture that may have been present. Following this, a water-resistant backing membrane was applied to one side of the specimens. After that, the samples were put through an incubation process that lasted for one hour and was carried out at a temperature of 370 degrees Celsius. A second measurement of the samples' weight was performed after the incubation period had concluded and the samples had been removed. The percentage of moisture that was absorbed was calculated by the use of a mathematical method.

Surface pH

To determine the surface pH, three films of each formulation were placed on an agar plate and allowed to swell for 2 hours. The surface pH was determined by placing pH paper on the swelling patch. The average of three readings was recorded.

B. PERFORMANCE PARAMETERS:

a) Drug content uniformity:

In order to determine the uniformity of the drug content, three film units of each formulation were placed into individual volumetric flasks that were 100 millilitres in capacity. After that, one hundred millilitres of phosphate buffer with a pH of 6.8 was added, and the mixture was stirred constantly for full twenty-four hours. After being filtered and diluted in the proper manner, the solutions were analysed with a UV spectrophotometer (Sysronic) at a wavelength of 229 nm. In order to arrive at the final result, the authors calculated the average amount of drug that was present in three different films.

b) Measurement of bioadhesive strength:

The amount of force needed to pull the bioadhesive strips away from the mucosal surface was used to measure how well the bioadhesives worked. The patch's ability to stick was tested using

a slightly different method, with the pig gut mucosa used as a model membrane. The instrument is a two-arm physical balance that has been changed so that the right pan is now held by a different shape. A pan for catching water that hangs from the left arm balances this out. A syphon tube was connected to a 10 L bottle that was set up high in the pan so that the water level in the bottle would always be higher than the level in the receiving pan. The flow is controlled by a device inside the syphon tube. Nylon thread was used to hang both the glass plate and the pan. A stage made of acrylate was attached to the glass beaker in the middle. A phosphate buffer solution (pH 6.8) was put into a glass beaker to make it look like spit in the body. A magnetic stirrer that can be set to a certain temperature was used to keep a phosphate buffer (pH 6.8) in a glass dish at 37±0.5 °C. Thread was used to securely connect a 3 cm long piece of pig gastric mucosa to the top of the acrylate tissue mounting stage. An adhesive was used to stick the pictures to the middle of the glass plate. The surface of the film was wet with phosphate buffer (pH 6.8) and left to soak up water and get bigger. Next, the film-covered glass plate was put on top of the mucosal tissue, which was firmly set up on the tissue mounting stage. The films were set up so that they could fully touch the mucosa. The whole assembly was left alone for a short time (called "preload time") so that the film and mucous tissue could stick to each other. The 50-gram glass plate was used as a preload. After the first step of getting ready, the water collecting pan was hung from the left arm and 200 drops of water per minute were added through the syphon tube until the film came off the mucosal surface. Under the water collection pan, a support was put in place to keep it in place while it was taken out. When the pan was taken off, the weight of the water that had gathered in it was weighed. Three times, the experiment was done.

Measurement of in vitro Residence Time

A modified USP disintegration device was used to measure the in vitro residence time. 800 ml of an isotonic phosphate buffer solution with a pH of 6.8 made up the breakdown medium. It was kept at 37±2°C, the temperature of the fluid. Each 3 cm piece of porcine buccal mucosa was attached to a glass slab, which was then linked to the apparatus vertically. An isotonic Phosphate buffer solution with a pH of 6.8 was used to wet one side of three mucoadhesive films from each batch. After being wet, the surface was put against the mucous barrier. The piece of glass was firmly attached to the machine in a vertical position and could move in that direction. In its lowest point, the film was fully buried in the buffer solution. In its highest point, it came out of the solution. It was written down how long it took for the film to fully wear away or separate from the nasal surface.

Scanning electron microscopy:

Scanning Electron Microscopy (SEM) has been utilised to ascertain the distribution of particle sizes, analyse the surface texture, and investigate the shape and structure of fractured or sectioned surfaces. The term "generally used" refers to the common practice of creating three-dimensional surface relief images by utilising secondary electrons. An analysis of the surface of polymeric drug delivery systems can yield valuable insights into the porosity and microstructure of the device.

Invitro release study by dissolution:

The spinning paddle method from the US Pharmacopoeia XXIII was used to study and figure out how the drugs released from the buccal patches. 500 ml of phosphate buffer was used as a dissolution medium. The temperature was 37±0.50c, and the speed of spinning was 50RPM. A dialysis sheet was used to cover patches that were cut out and had an area of 1 cm2. A glass slide was used to hold the assembly in place so it wouldn't move. The patch-filled dialysis membrane tube was held together at both ends with closure clips. Then, it was put at the bottom of the container that held a phosphate buffer with a pH of 6.8. Five millilitre samples were taken at regular times and replaced with new buffer medium. The samples were filtered using Whatman filter paper, and then they were looked at with a UV spectrophotometer at a 276nm range. Three times, the experiments were done, and the average numbers were found and shared.

Ex-vivo release study:

For ex-vivo release tests, buccal tissue from pigs that were gathered from an abattoir was used. A knife was used to cut away the fat and muscle tissue from the tissue, which was then put in a phosphate buffer solution with a pH of 7.4. The oral epithelial was carefully placed between two sections of a Franz diffusion cell that held 60ml of fluid. An acidic phosphate buffer (pH 7.4) was put into the sensor area. There was 4ml of phosphate buffer in the donor section, which was where the drug was dissolved. Everything was put on a magnetic mixer, and the temperature was kept at 37°C. The patch was moistened and stuck to the inside of the mouth. The epithelium of the buccal patch was put in the middle of the two sections. At set times, 3ml samples were taken from the receptor side and then replaced with a fresh buffer solution of the same size. At a wavelength of 229nm, a UV spectrophotometer was used to look at the materials.

Stability studies:

When a drug is kept in a certain container, its stability is measured by how well it keeps its physical, chemical, therapeutic, and toxicological properties within certain limits. The goal of stability testing is to find out how the quality of a drug substance or drug product changes over

time because of things like temperature, humidity, and light. This testing also helps figure out the best settings for storage. ICH says how long the study must last and how the samples must be stored:

Long term testing – 250c±20c/ 60%±5% RH for 12 months

Accelerated testing – 400c±20c/ 75%±5% RH for 6 months

Procedure:

In this study, stability tests were done on certain formulas for a set amount of time (90 days). For 30 days, the tests were done in an oven that managed the humidity and kept the temperature at 40°C ± 2°C and the relative humidity at 75% ± 5%. The chosen mixture, F3, was analysed to find out things about its physical properties, like its general surface pH and how much water it could hold. Performance factors such as drug content regularity, in vitro dissolution studies, and ex vivo permeation studies were also looked at.

Kinetic study:

No-order release rates were seen in the matrix systems, and drugs were released through diffusion. There were several models used to look at the data: zero order, first order, Higuchi matrix, and Peppa's model. These models helped us figure out how the dosage form worked and how fast it delivered the medicine. Using the rvalues to compare them, the best fit model was chosen.

1. Zero order kinetics:

The following equation shows how drugs dissolve from pharmaceutical dose forms that don't break apart and release the drug slowly. This is based on the idea that the surface area stays the same and that balance is never reached.

$$Qt = Qo + Kot$$

The zero-order releasing constant is Ko, and Qt is the amount of drug that was dissolved in time t. Qo is the amount of drug that was in the solution at the start.

2. First order kinetics:

These release rate measurements were matched to the equation that follows to investigate the first order release kinetics.

$$\text{Log } Qt = \log Qo + k1t/2.303.$$

To find K1, we need to know how much of the drug was in the solution at time t, how much was released at time t, and how much was in the solution at the start.

3. Higuchi model:

Higuchi came up with a number of theoretical models to look into how drugs that are partially or fully dissolved in water are released from semisolid or solid media. To explain the behaviour of drug particles spread out in a uniform matrix that acts as the diffusion medium, mathematical equations were created. Here's how the equation works:

$$Qt = KH.\ t1/2$$

Where Qt is the amount of drug released in time t, KH is the Higuchi dissolution constant.

4. Korsmeyer and Peppa's model:

The following equation is used to fit the release rate data to this model so that it can be studied.

$$Mt/M\_ = K.tn$$

These numbers show the drug's fractional release (Mt/M_), its release constant (K), its release time (t), and its diffusional exponent (n), which changes depending on the shape of the matrix dose form.

6. RESULTS

6.1 Preformulation studies:

The preformulation studies were performed for drug for following parameters:

1. Solubility
2. Determination of pH
3. Density
4. Carr's Index (I)
5. Angle of repose
6. Particle size analysis using stage micrometer.

Solubility

The known quantity of solute was dispersed in the solvent like water, cold water, hot water, 0.1 N NaOH, 0.1 HCl, phosphate buffer 6.2, phosphate buffer 6.4, phosphate buffer 7.4, organic solvents like n-hexane, and solubility was determined.

Table No. 4: Solubility of Pantoprazole Sodium with Different Solvents.

S.No.	Solvents used	Solubility
1	Water	Freely soluble
2	Hot water (60^0C)	Freely soluble
3	Cold water (10^0C)	Very soluble
4	0.1 N NaOH	Soluble
5	0.1 N HCl	Sparingly Soluble
6	Phosphate buffer 6.2	Very slightly soluble
7	Phosphate buffer 6.4	Insoluble
8	Phosphate buffer 7.2	Insoluble
9	n-hexane	Insoluble

Determination of pH:

A 2%w/v solution of drug was prepared using water as a solvent. The pH meter was previously calibrated with standard buffer solution. The glass electrode of the pH meter was immersed in the prepared solution and the pH of the corresponding solution was recorded.

Table No. 5: Preformulation Studies Parameters:

S.No.	Parameters	Values
1	Solubility	Freely soluble in water, very slightly soluble in phosphate buffer pH7.4 and insoluble in n-hexane
2	Bulk Density	0.39 g/ml
3	Tapped density	0.326 g/ml
4	Carr's Index	6.13±0.12
5	Angle of repose	25.79±0.24

6	pH	9.9 (2% solution)
7	Avgas Particle size	0.498±0.051

DRUG ANALYSIS:

The drug analysis of the Aliskerin was performed for its:

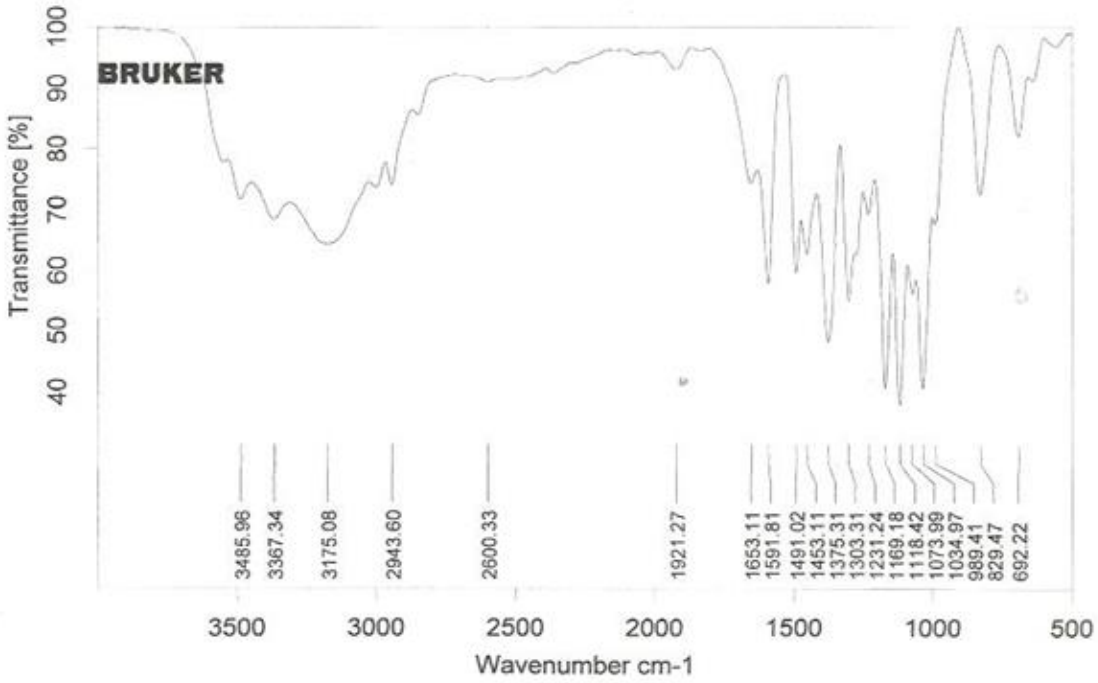
1. General appearance
2. Colour
3. Texture
4. Odour
5. Melting point

Table No. 6: Drug Analysis Parameters

S. No.	Parameters	Inference
1	General appearance	Crystalline powder
2	Colour	White to off-white
3	Odour	None
4	Texture	Smooth
5	Melting point	99 ºC

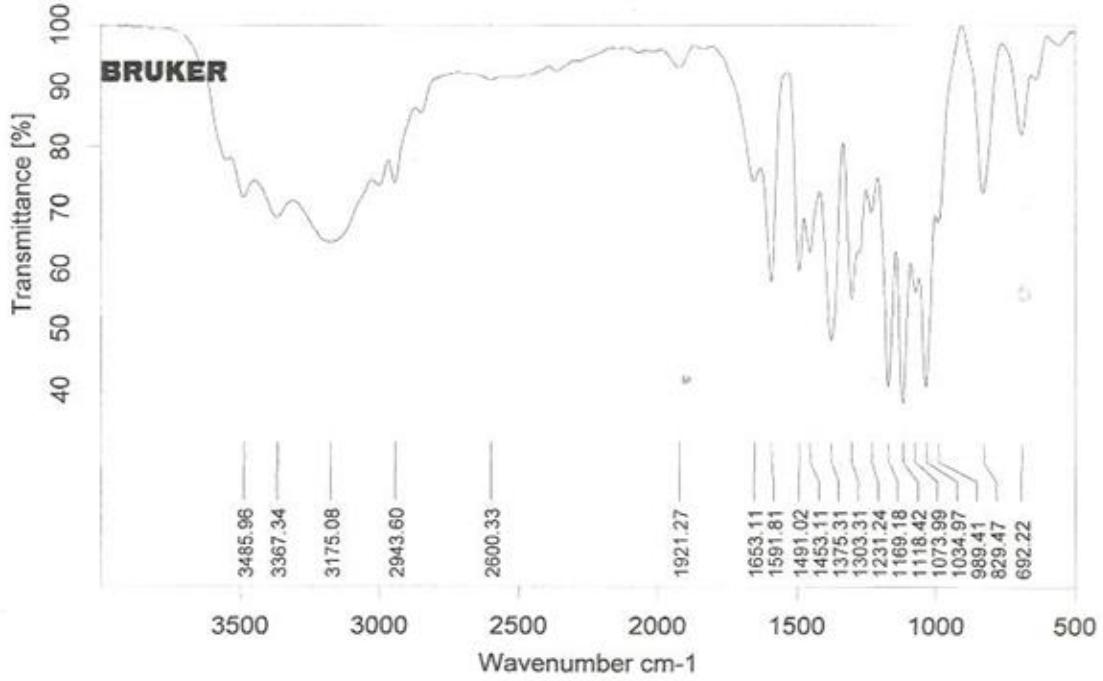
Compatibility Studies:

The Compatibility studies of the drug and drug excipients were carried out to check the compatibility between the drug and the excipients. This was done using FT-IR. The binary mixtures (1:1) of all the excipients with drug were formed by trituration in a mortar and pestle to form a uniform mixture and to identify if any physical incompatibility is there. The binary mixtures are then exposed to FT-IR analysis.



Wavenumber	Abs. intensity	Rel. intensity	Width	Found if threshold <	Shoulder
3485.9619	0.717	0.045	535.2446	4.319929	0
3367.3369	0.684	0.052	672.3003	4.314996	0
3175.0821	0.643	0.344	665.4650	51.993187	0
2943.5962	0.740	0.040	23.4532	5.784724	0
2600.3249	0.909	0.018	1181.4924	1.945567	0
1921.2669	0.930	0.035	61.4121	5.275044	0
1653.1085	0.743	0.040	97.2789	3.279591	0
1591.8078	0.578	0.345	46.4998	55.302048	0
1491.0231	0.596	0.257	167.4507	20.873022	0
1453.1140	0.627	0.070	24.2331	8.893753	0
1375.3133	0.482	0.328	48.1530	52.247433	0
1303.3135	0.550	0.243	57.3666	31.907118	0
1231.2365	0.693	0.044	21.6904	5.724521	0
1169.1832	0.407	0.224	25.4905	35.536842	0
1118.4181	0.379	0.620	211.6524	99.881531	0
1073.9850	0.561	0.034	67.8514	3.766995	0
1034.9714	0.406	0.321	219.9267	32.595196	0
989.4097	0.676	0.046	94.9490	1.720772	0
829.4711	0.724	0.273	56.4898	42.659901	0
692.2243	0.821	0.155	48.3257	24.094761	0

Fig. No. 5: FTIR Spectra of Aliskerin



Wavenumber	Abs. intensity	Rel. intensity	Width	Found if threshold <	Shoulder
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1653.1085	0.743	0.040	97.2789	3.279591	0
1591.8078	0.578	0.345	46.4998	55.302048	0
1491.0231	0.596	0.257	167.4507	20.873022	0
1453.1140	0.627	0.070	24.2331	8.893753	0
1375.3133	0.482	0.328	48.1530	52.247433	0
1303.3135	0.550	0.243	57.3666	31.907118	0
1231.2365	0.693	0.044	21.6904	5.724521	0
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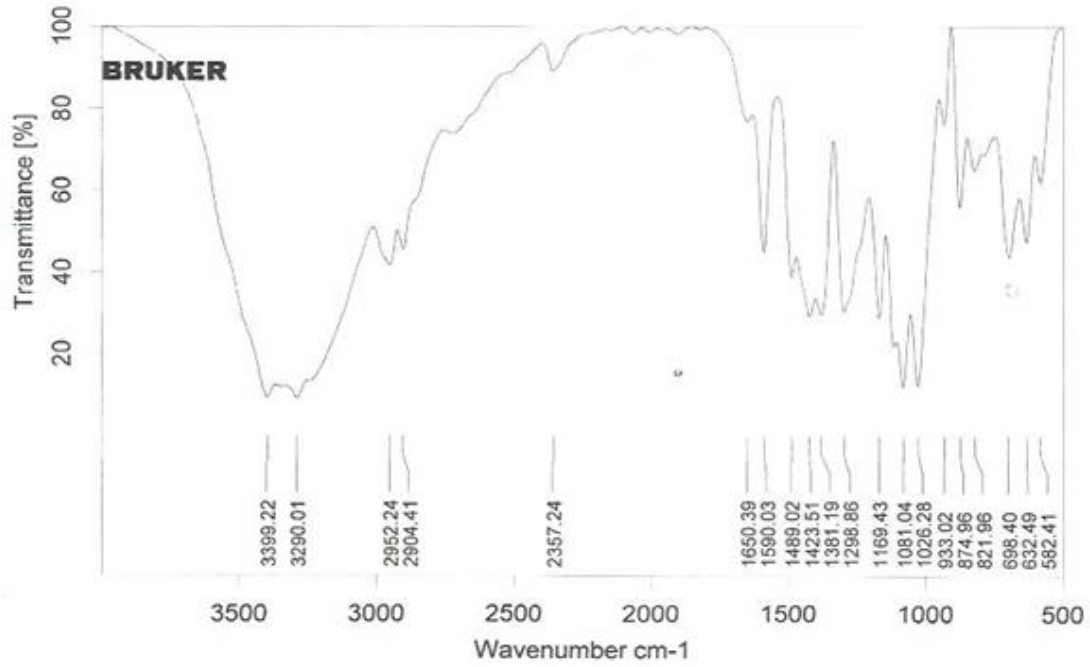
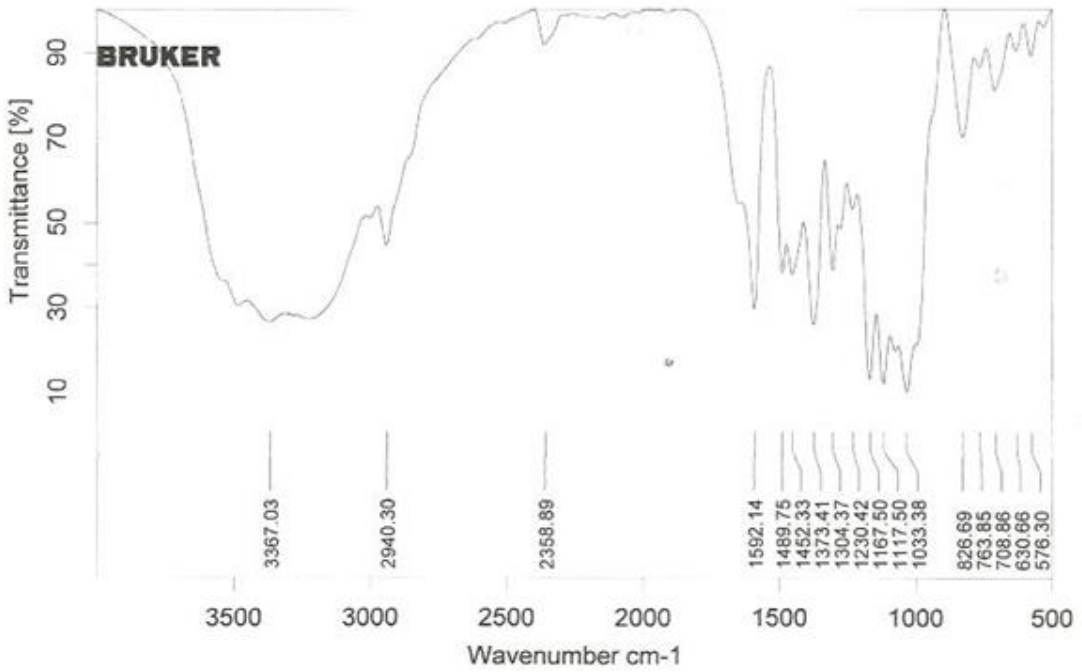
989.4097	0.676	0.046	94.9490	1.720772	0
829.4711	0.724	0.273	56.4898	42.659901	0
692.2243	0.821	0.155	48.3257	24.094761	0

Fig. No. 6: FTIR Spectra of Aliskerin and Okra Gum



Wavenumber	Abs. intensity	Rel. intensity	Width	Found if threshold <	Shoulder
3399.2198	0.095	0.078	0.3118	3.421093	0
3290.0124	0.094	0.906	701.8368	99.996025	0
2952.2420	0.417	0.117	63.6483	10.161175	0
2904.4064	0.456	0.053	22.8012	4.866379	0
2357.2435	0.892	0.071	55.9211	7.476027	0
1650.3888	0.768	0.035	197.1720	1.860740	0
1590.0329	0.450	0.405	38.1966	41.815754	0
1489.0188	0.388	0.074	149.6441	5.392353	0
1423.5111	0.293	0.476	151.2369	47.298141	0
1381.1901	0.298	0.160	117.9860	4.242686	0
1298.8614	0.304	0.379	399.0735	30.694544	0
1169.4271	0.289	0.220	26.1160	22.311419	0
1081.0381	0.121	0.879	213.2584	96.999352	0
1026.2762	0.123	0.312	165.5604	19.366056	0
933.0157	0.764	0.132	49.9805	6.494036	0
874.9546	0.559	0.388	109.8859	19.281370	0
821.9548	0.650	0.081	49.8881	8.791299	0
698.3959	0.438	0.562	173.1505	61.917782	0
632.4868	0.476	0.174	173.2857	11.743525	0
582.4084	0.620	0.130	110.9852	7.450516	0

Fig. No. 7: FTIR Spectra of Aliskerin and HEC



Wavenumber	Abs. intensity	Rel. intensity	Width	Found if threshold <	Shoulder
3367.0275	0.266	0.734	771.4281	81.503975	0
2940.2968	0.444	0.106	33.2805	10.316204	0
2358.8867	0.918	0.082	58.8039	9.132796	0
1592.1361	0.296	0.593	90.1532	63.282711	0
1489.7526	0.381	0.181	131.4005	7.343583	0
1452.3299	0.376	0.248	439.4315	13.675836	0
1373.4097	0.258	0.415	51.0755	43.030270	0
1304.3735	0.387	0.240	54.2551	22.726830	0
1230.4159	0.531	0.047	298.7720	3.909262	0
1167.5029	0.131	0.176	25.7386	16.846962	0
1117.4964	0.121	0.136	26.8047	12.357558	0
1033.3819	0.101	0.899	242.7574	99.965797	0
826.6912	0.701	0.295	63.4461	30.241974	0
763.8536	0.864	0.033	118.4208	2.659435	0
708.8620	0.810	0.110	43.4044	11.099729	0
630.6635	0.904	0.052	30.3381	4.535875	0
576.3042	0.893	0.078	27.3230	8.436538	0

Fig. No. 8: FTIR Spectra of Aliskerin and PVP

Calibration curve of Aliskerin using UV spectrophotometer:

The calibration curve of the drug was prepared to set the purity standards of the drug in suitable solvents.

A. Instrument and apparatus

Shimadzu 1700 UV-Visible Spectrophotometer model was used for spectral measurements with spectral band width 1 nm; wavelength accuracy is 0.5 nm and 1 cm matched quartz cells. Glassware used in each procedure were rinsed thoroughly with double distilled water and dried in hot air oven.

B. Reagents and Materials

All chemicals were of analytical reagent grade and double distilled water was used to prepare solutions.

1. Standard drug solution

A stock standard solution equivalent to 1mg/ml drug was prepared by dissolving 50 mg of pure drug in water and diluting to 50 ml in calibrated flask with water.

2. Sub Stock solution

To prepare the sub stock solution, 5ml from the standard stock solution was taken and diluted up to 50ml in calibrated flask with water.

C. Method

Different aliquots (0.5 to 3.5 ml) of sub-stock solution of Aliskerin were taken in volumetric flasks of 10ml and the final volume was made up with water. Then all dilutions were scanned between 200-400 nm against blank which shows the maximum absorbance at292 nm.

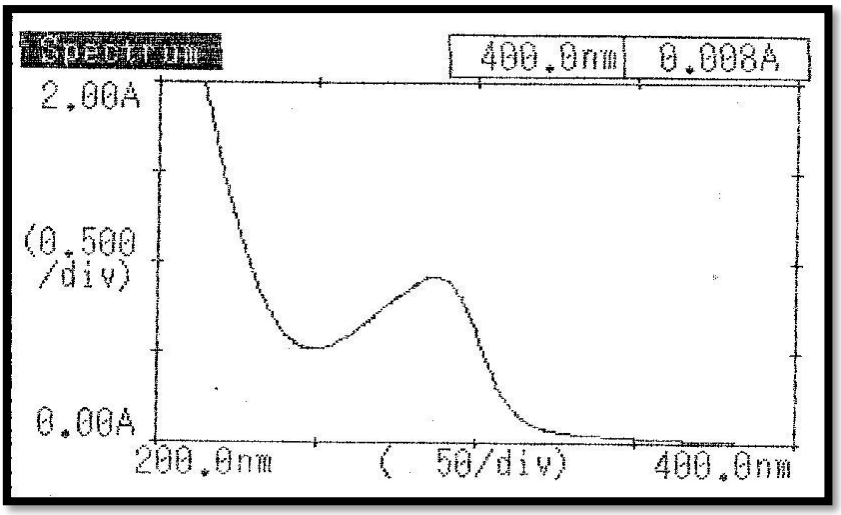


Fig. No. 9: UV Spectra of Aliskerin

Table No. 7: Observation Table of Calibration curve of Aliskerin

S.No.	Concentration(ug/ml)	Absorbance
1	0.5	0.06
2	1.0	0.12
3	1.5	0.182
4	2.0	0.237
5	2.5	0.306
6	3.0	0.365

The same λ max was used for further measurement of drug. A calibration curve for absorbance vs. concentration was plotted. The plot is as follows:

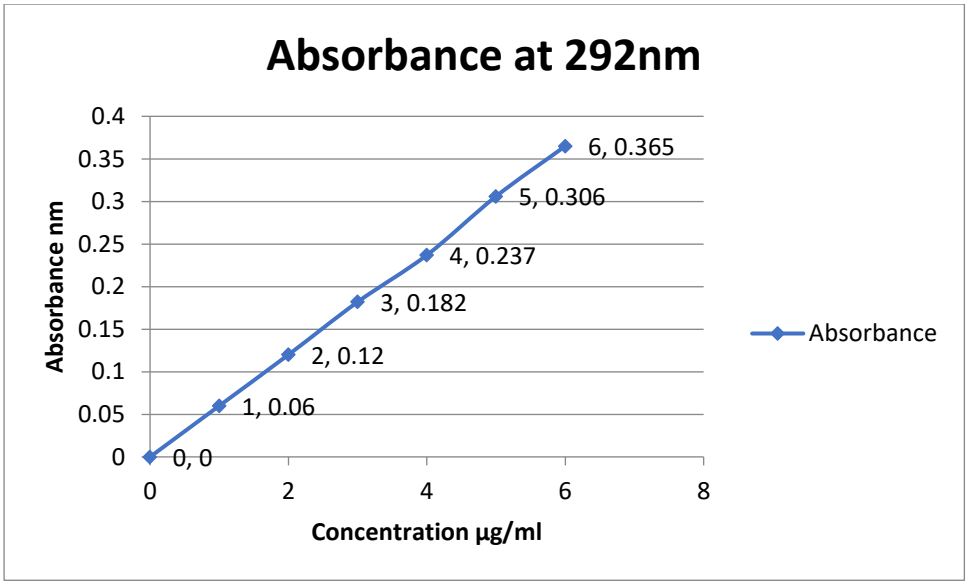


Fig. No.10: Standard Curve of Aliskerin

EVALUATION PARAMETERS:

Physical properties:

Thickness of patch: The thickness of the prepared buccal patches of each formulation was determined within the range of 0.19± 0.004 to 0.28± 0.012 mm.

Folding endurance: The folding endurance of each formulation was determined within the range of 286± 4.80 to 316± 4.52.

Mechanical strength: Three patches of each formulation were evaluated and mean values are recorded. The values were found to be in the range of 7.02± 0.042 to 15.22± 0.064 kg/mm^2. The values revealed that the patches were having good mechanical strength.

Water uptake study: Water uptake of all buccal patches containing drug is measured. These values represent the mean of three replicate determinations. The values were found to be within the range of 1.42± 0.24 to 3.44± 0.24. The percentage water absorption of the respective patches was determined at Third hour.

Table No. 8: Physical Evaluation of different Patches

Formulation Code	Physical Parameters of Buccal patch			
	Thickness (mm)±SD (n=3)	Folding endurance (mm)±SD (n=3)	Mechanical Strength (mm)±SD (n=3)	Water Uptake (mm)±SD (n=3)
F1	0.19± 0.004	298± 8.06	6.14± 0.062	3.05± 0.55
F2	0.24± 0.012	295± 6.02	7.02± 0.042	2.44± 0.82
F3	0.25± 0.010	286± 4.80	14.24± 0.082	1.42± 0.24
F4	0.28± 0.012	294± 5.40	10.52± 0.034	3.44± 0.24
F5	0.22± 0.011	302± 6.46	11.68± 0.12	1.82± 0.054
F6	0.20± 0.012	300± 4.20	8.42± 0.066	1.5± 0.15
F7	0.28± 0.018	310± 5.25	8.22± 0.42	3.02± 0.456
F8	0.28± 0.014	316± 4.52	10.44± 0.044	3.24± 0.64
F9	0.28± 0.028	305± 6.60	15.22± 0.064	2.96± 0.144
F10	0.26± 0.019	301± 8.20	10.24± 0.076	2.98± 0.58

Performance parameters:

Table No. 9: Bio adhesive Performance

Formulation Code	Bio adhesive Performance		
	Bioadhesive strength(gms)± S.D (n=3)	Force of adhesion (N) ± S.D (n=3)	Bond strength ± S.D (kg/mm2) (n=3)
F1	4.12± 0.12	6.1± 0.14	315±15.55

F2	3.94± 0.28	5.92± 0.18	325±10.5
F3	4.5± 0.05	6.34± 0.62	332±8.6
F4	3.72± 0.36	5.94± 0.88	319±9.25
F5	3.12± 0.16	5.36± 0.82	305±10.25
F6	3.92± 0.06	5.40± 0.22	325±8.5
F7	3.79± 0.10	5.82± 0.32	328±9.4
F8	3.75± 0.05	5.16± 0.34	330±10.45
F9	3.68± 0.26	5.55± 0.5	322±9.56
F10	3.56± 0.16	5.85± 0.15	305±10.45

***In vitro* release study:**

Table No. 10: *In vitro* release study

Time (Hours)	**% Cumulative Drug Release of different formulations**									
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**
0	0	0	0	0	0	0	0	0	0	0
0.5	12.45	14.34	10.75	12.66	11.35	13.24	11.65	14.28	13.67	14.22
1	22.14	26.56	19.34	21.35	21.14	25.55	20.14	23.5	20.24	25.45
2	35.25	39.40	32.18	35.68	34.28	38.16	33.16	37.28	28.15	38.30
3	46.22	51.24	42.12	44.26	45.24	50.34	44.22	46.46	35.46	50.14
4	64.32	68.46	54.22	56.08	64.12	64.26	56.12	58.18	44.42	67.36
5	75.12	80.14	66.15	69.5	78.22	75.12	68.25	70.52	56.5	79.14
6	84.56	90.22	74.28	80.34	86.58	85.22	76.24	84.24	66.86	89.22
7	91.15	98.13	85.56	92.14	95.18	94.16	84.46	94.64	76.45	97.18
8	98.22	99.5	96.24	98.56	99.82	99.98	98.12	99.16	88.78	99.34

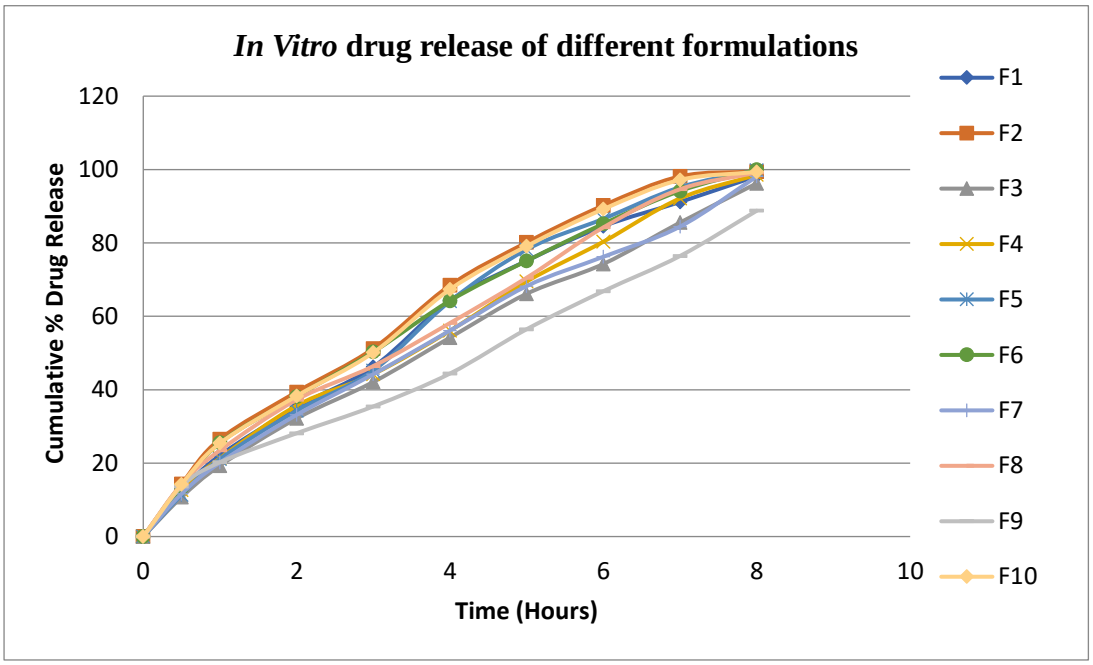


Fig. No. 11: *In Vitro* drug release of different formulations

Drug Release Kinetics

Table No. 11: Drug Release Kinetics

Formulation Code	Zero Order r^2 Value	First Order r^2 Value	Higuchi r^2 Value	Korsmeyer peppas r^2 Value	n Value
F1	0.9776	0.8836	0.9227	0.9968	0.7542
F2	0.9649	0.8685	0.9213	0.9942	0.7077
F3	0.9928	0.8608	0.9187	0.999	0.7787
F4	0.9897	0.8284	0.9169	0.9977	0.7406
F5	0.9792	0.7598	0.9249	0.9956	0.7989
F6	09763	0.6255	0.9201	0.9958	0.7188
F7	0.9895	0.7911	0.9185	0.9993	0.7576
F8	0.9852	0.8201	0.9152	0.9968	0.7038

F9	0.9905	0.9052	0.9060	0.9772	0.6644
F10	0.9688	0.8735	0.9211	0.9955	0.7141

CHAPTER-7

SUMMARY AND CONCLUSION

Aliskiren is a medication used to treat high blood pressure. It belongs to a group of drugs called direct renin inhibitors, which work by reducing certain natural chemicals that constrict blood vessels. This relaxation of the blood vessels helps the heart to pump blood more efficiently. Traditional doses of Aliskiren release the drug quickly, causing the therapeutic levels in the blood to drop shortly after administration, necessitating frequent dosing. To address this issue, researchers developed a controlled-release drug delivery system using mucoadhesive buccal patches. These patches are designed to release the drug slowly over eight hours, maintaining therapeutic levels for a longer period and reducing the need for frequent dosing. The mucoadhesive buccal patches were made using a combination of okra gum, hydroxyethyl cellulose (HEC), polyvinyl alcohol (PVA), and polyvinylpyrrolidone (PVP) as the matrix-forming agents. Propylene glycol was used as a plasticizer to give the patches flexibility. Fourier transform infrared spectroscopy (FTIR) was used to ensure that there were no interactions between the drug, polymers, and other excipients, confirming the stability of the formulation. The patches were prepared using a solvent casting method, which involves dissolving the ingredients in a solvent, mixing them thoroughly with a magnetic stirrer, and then casting the solution into molds to form patches. Once the patches were prepared, they underwent various evaluations to assess their quality and effectiveness. These tests included measuring thickness, folding endurance (to see how well they could bend without breaking), weight variation, water uptake, bioadhesive strength (how well they stick to the mucous membranes), mechanical strength, surface pH, and drug release properties through in-vitro studies. Among the different

formulations tested, formulation F3 stood out as the best. It exhibited good bioadhesive strength, controlled drug release, and favorable results in all other tested parameters. Formulation F3 was able to release the drug steadily over eight hours, achieving the goal of maintaining therapeutic concentrations for a longer duration. This extended release helps in reducing the frequency of dosing, making the treatment more convenient for patients.

To understand the drug release mechanisms, the formulations were analyzed using four different kinetic models: Zero order, First order, Higuchi matrix, and Peppas model equations. All formulations fit best into the Peppas model, which suggested that the drug release followed a combination of diffusion and erosion mechanisms. The diffusional exponent (n) values for these formulations ranged between 0.6 and 0.9, indicating this dual mechanism of drug release. Thus, the development of controlled-release mucoadhesive buccal patches for Aliskiren represents a significant advancement in drug delivery for high blood pressure treatment. By using a combination of specific polymers and plasticizers, the researchers were able to create a stable dosage form that releases Aliskiren over an extended period. Formulation F3, in particular, proved to be the optimal choice, demonstrating consistent drug release and strong bioadhesive properties. This innovation not only enhances the efficiency of the drug but also improves patient compliance by reducing the need for frequent dosing. Thus, the study successfully highlights the potential for developing effective controlled-release systems for other medications as well, using similar methodologies.

CONCLUSION

To sustain steady therapeutic levels of the medication for an extended period of time, an innovative muccoadhesive drug delivery system has been developed in the current

study. The drug delivery system takes the shape of buccal patches that release Aliskiren in a bidirectional fashion. Drug release, bioadhesive strength, content homogeneity, percentage water absorption, surface PH, thickness, and mechanical strength were all achieved to a satisfactory degree in buccal formulations of Aliskiren in the form of muccoadhesive patches. Although the outcomes from all buccal patches were satisfactory, the optimal formulation F3, which included okra gum, had the best results. According to in-vitro dissolving investigations of the optimised formulation, the diffusion and erosion mechanisms appeared to be responsible for the percentage cumulative drug release from the patches in this work. The non-Fickian nature of the discharge pattern was observed. According to the above study, there is a chance that a mucoadhesive drug delivery system for lithium den will be developed. This system will likely be more effective and well-liked than the current one, and it will also likely have a controlled release profile that will allow for higher therapeutic efficacy.

References

1. Zaharuddin ND, Noordin MI, Kadivar A. The Use of Hibiscus esculentus (Okra) Gum in Sustaining the Release of Propranolol Hydrochloride in a Solid Oral Dosage Form. Biomed Res Int [Internet]. 2014 [cited 2024 Aug 6];2014. Available from: /pmc/articles/PMC3942280/

2. Kaur G, Singh D, Brar V. Bioadhesive okra polymer based buccal patches as platform for controlled drug delivery. Int J Biol Macromol [Internet]. 2014 [cited 2024 Aug 6];70:408–19. Available from: https://pubmed.ncbi.nlm.nih.gov/25036601/

3. Gilhotra RM, Ikram M, Srivastava S, Gilhotra N. A clinical perspective on mucoadhesive buccal drug delivery systems. J Biomed Res [Internet]. 2014 [cited 2024 Aug 6];28(2):81. Available from: /pmc/articles/PMC3968279/

4. Alqahtani MS, Kazi M, Alsenaidy MA, Ahmad MZ. Advances in Oral Drug Delivery. Front Pharmacol [Internet]. 2021 Feb 19 [cited 2024 Aug 6];12. Available from: /pmc/articles/PMC7933596/

5. Chinna Reddy P, Chaitanya KSC, Madhusudan Rao Y. A review on bioadhesive buccal drug delivery systems: current status of formulation and evaluation methods. DARU J Pharm Sci [Internet]. 2011 [cited 2024 Aug 6];19(6):385. Available from: /pmc/articles/PMC3436075/

6. Aslani A, Ghannadi A, Najafi H. Design, formulation and evaluation of a mucoadhesive gel from Quercus brantii L. and coriandrum sativum L. as periodontal drug delivery. Adv Biomed Res. 2013;2(1):21.

7. Alkilani AZ, McCrudden MTC, Donnelly RF. Transdermal Drug Delivery: Innovative Pharmaceutical Developments Based on Disruption of the Barrier Properties of the stratum corneum. Pharmaceutics [Internet]. 2015 Oct 22 [cited 2024 Jul 2];7(4):438. Available from: /pmc/articles/PMC4695828/

8. Pons-Faudoa FP, Ballerini A, Sakamoto J, Grattoni A. Advanced implantable drug delivery technologies: transforming the clinical landscape of therapeutics for chronic diseases. Biomed Microdevices [Internet]. 2019 May 5 [cited 2024 Aug 6];21(2):47. Available from: /pmc/articles/PMC7161312/

9. Hua S. Advances in Oral Drug Delivery for Regional Targeting in the Gastrointestinal Tract - Influence of Physiological, Pathophysiological and Pharmaceutical Factors. Front Pharmacol [Internet]. 2020 Apr 28 [cited 2024 Aug 6];11. Available from: /pmc/articles/PMC7212533/

10. Alghanem S, Dziurkowska E, Ordyniec-Kwaśnica I, Sznitowska M. Intraoral medical devices for sustained drug delivery. Clin Oral Investig [Internet]. 2023 Dec 1 [cited 2024 Aug 6];27(12):7157. Available from: /pmc/articles/PMC10713785/

11. Bartlett JA, Van Der Voort Maarschalk K. Understanding the Oral Mucosal Absorption and Resulting Clinical Pharmacokinetics of Asenapine. AAPS PharmSciTech [Internet]. 2012 Dec [cited 2024 Aug 6];13(4):1110. Available from: /pmc/articles/PMC3513449/

12. Jacob S, Nair AB, Boddu SHS, Gorain B, Sreeharsha N, Shah J. An Updated Overview of the Emerging Role of Patch and Film-Based Buccal Delivery Systems. Pharmaceutics [Internet]. 2021 Aug 1 [cited 2024 Aug 6];13(8). Available from:

/pmc/articles/PMC8399227/

13. Manohar SD, Sridhar DA, Mallikarjuna SC. Drug delivery from the oral cavity: A focus on mucoadhesive buccal drug delivery systems. PDA J Pharm Sci Technol. 2012;66(5):466–500.