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"FORMULATION AND EVALUATION OF MUCOADHESIVE BUCCAL FILMS CONTAING OF FAMOTIDINE: A NOVEL APPROCH FOR ENHANCED DRUG DELIVERY"

Lalam Ramanamma, Naredla Sai sri Harshitha, Malla Siddu, Rudra prasad tripathy

Assistant Professor, student

Raghu college of Pharmacy

ABSTRACT

Buccal cavity suggests a suitable route of administration for a systemic delivery of a drug. The as mucoadhesive buccal film provide on set of action in oral cavity. Famotidine is an H2 receptor antagonist which is used as an anti-ulcer agent in the treatment of peptic ulcers. The present exploration focuses on formulating Famotidine as mucoadhesive buccal film to treat the mouth ulcers. These are formulated as films to overcome the problems associated with its oral delivery, to avoid first pass effect and to improve its bioavailability. These buccal films were formulated by using solvent casting technique by using HPMC, PVP as a polymer. The physicochemical characteristics of the films were evaluated. The formulated films exhibited satisfactory mechanical properties with good mucoadhesive strength. The in vitro drug release studies show sustained release of Famotidine. The ex vivo permeation studies showed buccal films enhanced the permeation of Famotidine compared to an oral solution. The developed mucoadhesive buccal film of Famotidine shows potential as an alternative dosage form for improved localized drug delivery in the treatment of gastrointestinal disorder.

Keywords: Famotidine, Bucco adhesive film, In vitro release, Evaluation, bioavailability, oral mucosa, H2 antagonist.

INTRODUCTION

Buccal route of administration provides rapid on set of action and increase bioavailability of the drug. It evades pre-systemic metabolism and contact of drugs with gastrointestinal fluids [1]. The oral mucosa has high absorptive capacity with more blood supply and produce prolonged action through the mucosal membrane [2]. The drugs which have high permeability for local action sublingual route is preferred.

Buccal films which dissolve on the patient's buccal mucosa is a special technique in drug delivery. Their thinness enhances patient compliance compared to lozenges and tablets. The pharmaceutical industry is more focused on buccal films as they seem to be patient-friendly and practical dosage forms. [3,4]

Mucoadhesive buccal films represent a novel dosage form that evades first-pass metabolism, showing rapid onset of action and enhanced patient compliance. Patients prefer mucoadhesive buccal films over buccal tablets due more flexibility that provides comfort. [3,5]

Ideal characteristics of films [6]

1. The films should have a pleasant taste.
2. Drugs should be highly resistant to moisture and soluble in saliva.
3. It should have the right amount of tension.
4. It should be ionized at the pH level of the oral cavity.
5. It should be able to penetrate the oral mucosa.
6. It should have a fast-acting effect.

Famotidine is H2 blocker, it is histamine H2 receptor antagonist which decreases acid production majorly used in the treatment of gastric and duodenal ulcers and gastroesophageal reflux disease [2]. It acts by blocking the action of histamine on parietal cells of the stomach and decrease the amount of gastric acid secretion. It is also used to treat Zollinger-Ellision syndrome. The systemic bioavailability of famotidine is only 40-45% due to first pass effect. So, the current exploration studies call attention to buccal route of administration of famotidine to skip the first pass metabolism and reduce dose, increase bioavailability and prolonged action [1].

Famotidine is conveniently showing buccal absorption and provide more pharmacological activity, hence can be formulated as mucoadhesive buccal film [2]. The drugs whose prescribed dose is 40mg or less can be administered in oral route.

The film was formulated using solvent casting technique which is more preferably used and cost-effective process in the manufacturing of pharmaceutical films. The polymers used in the process are hydroxy propyl methyl cellulose [HPMC], poly vinyl pyrrolidine [PVP] and propylene glycol as a plasticizer and ethanol as a solvent.[1]

Advantages of buccal films [3,6,7,8,9]

- Easy for administration
- Low dose shows effective action and lesser side effects.
- Bypass 1st pass metabolism
- Does not require water for use
- Prolonged contact with mucosa can enhance the effectiveness of drugs.
- Improved API bioavailability
- It can be easily administered by patients mentally ill
- Buccal mucosa has very rich blood supply and also permeable.
- Passive absorption mechanism by paracellular transport
- Due to adhesion and intimate contact of drug improves absorption
- Less aqueous solubility
- Suitable alternative route for steroids, analgesics, enzymes, hormones.

Disadvantages of buccal films [3,6,7,8,9]

- Area available for absorption of drug is limited.
- There may be loss of some amount of drug due to saliva.
- Only passively diffused can be applied.
- Require special packing materials

- Hygroscopic nature
- Not suitable for drugs that cause irritation or allergies in oral mucosa.

MATERIALS AND METHOD [1, 2]

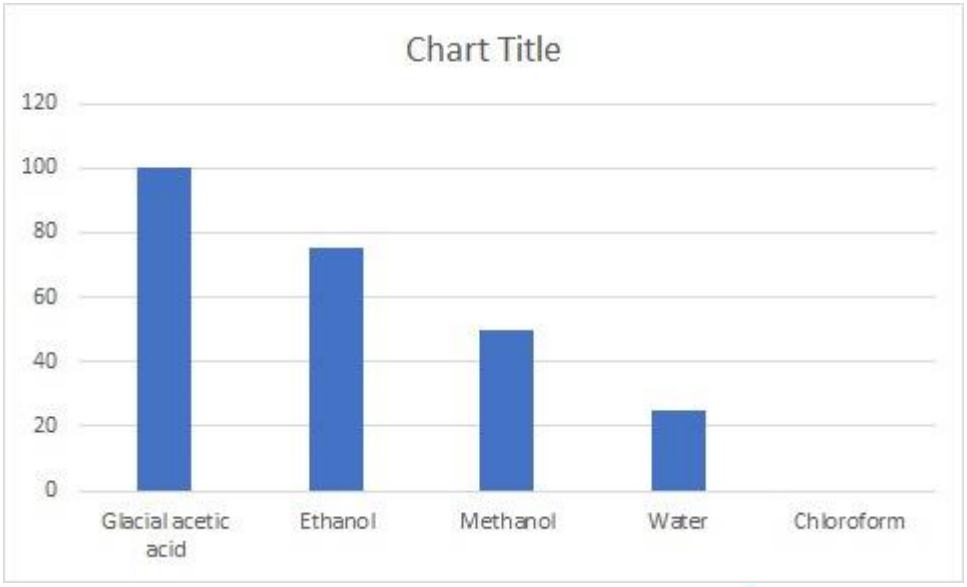
Famotidine, HPMC (Hydroxy propyl methyl cellulose), PVP (poly vinyl pyrrolidine), propylene glycol.

Famotidine was obtained as a gift sample from HETERO LABS, HYDERABAD.
Propylene Glycol
Hydroxypropyl methylcellulose (HPMC 15 cps and 50 cps) were produced from CDH Laboratories, New Delhi
Polyvinyl pyrrolidine
Ethanol
All other chemicals used were of analytical grade.

SOLUBILITY STUDIES OF FAMOTIDINE

S.NO	TEST	OBSERVATION	INFERENCE
1.	Famotidine in glacial acetic acid	Clear solution formed	Completely soluble
2.	Famotidine in Ethanol	Solution formed	Slightly soluble
3.	Famotidine in Methanol	White precipitate formed	Very slightly soluble
4.	Famotidine in water	White precipitate formed	Very slightly soluble
5.	Famotidine in chloroform	White powder settled down	Completely in soluble

➢ Ethanol is selected as a suitable solvent in this process because both drug and polymer are soluble in ethanol and it shows effective results in formulating a film.
➢ Glacial acetic acid, though the drug is completely soluble, but due to its poor drying property it is not suitable for formulating a film.



Solubility of famotidine in different solvents

METHODOLOGY

The solvent casting method is widely used in casting because it's simple and cost-effective. It works by mixing a polymer and plasticizer in a solvent like ethanol or acetone, then letting the solvent evaporate either at room temperature or under controlled conditions. This creates a film with the polymer chains and plasticizer molecules. Drugs can also be added to the solution, either suspended or dissolved, before casting the film. [10,11]

CHEMICALS USED: [1,2]

Drug: Famotidine

Polymers: HPMC, PVP.

Solvent: 70% Ethanol

Plasticizer: 30% propylene glycol

Solvent casting technique [1]

Solvent Casting Technique for Famotidine Films:

1. **Preparation of polymer mixture**: Dissolve polymers in a suitable solvent.

2. **Addition of Famotidine:** Disperse 2mg of famotidine in the polymeric solution along with propylene glycol (acting as a plasticizer and penetration enhancer).

3. **Mixing:** Thoroughly mix the solutions until they reach a semi-solid consistency.

4. **Deaeration**: Use a bath sonicator to remove air bubbles from the solution.

5**. Casting:** Pour the solution into petri plate and cover them with funnels to control evaporation.

6. **Drying:** Allow the films to dry at room temperature overnight.

7. **Packaging:** After drying, separate the films and pack them in aluminium foil.

Storage Conditions:

Store the films in a desiccator at room temperature and 58% relative humidity.

Figure 1

Selection of polymers

↓

Selection of solvent

↓

Preparation of polymer solution

↓

Addition of plasticizer

↓

Addition of drug substance

↓

Casting of film

↓

Solvent evaporation

↓

Film drying

↓

Film characterization

↓

Storage under controlled conditions

By using solvent evaporation technique/ solvent casting technique we prepare the films. By using various polymers such as HPMC and PVP of various composition [2], 30% propylene glycol as a plasticizer, 70% ethanol as a solvent [1].

PROCEDURE [2]

Preparation on film 1,

In the first formulation to the 2mg of the famotidine add the HPMC and PVP polymers with a composition of 1.5gm and 0.5gms which is soluble in the solvent 10 ml ethanol. Then add 0.5ml of propylene glycol as plasticizer.

Preparation on film 2,

In the second formulation to the 2mg of the famotidine add the HPMC and PVP polymers with a composition of 1:1 ratio which is soluble in the solvent 10ml of ethanol. Then add 0.5ml of glycol as plasticizer.

Preparation on film 3,

In the third formulation to the 2mg of famotidine add the HPMC and PVP polymers with the composition of 0.5gm and 1.5gms which is soluble in the solvent 10ml of ethanol. Then add 0.5ml of propylene glycol is used as plasticizer.

Preparation on film 4,

In the fourth formulation to the 2mg of famotidine add the PVP polymer with the composition of 2gm which is soluble in the solvent 10ml of ethanol. Then add 0.5ml of propylene glycol is used as plasticizer.

Preparation on film 5,

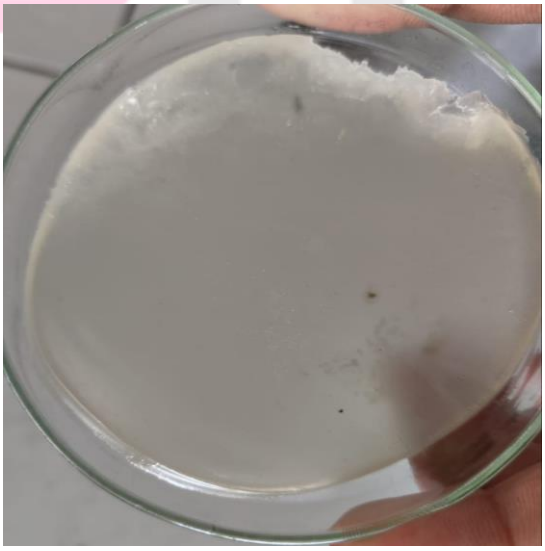
In the fifth formulation to the 2mg of famotidine add the HPMC polymer with the composition of 2g which is soluble in the solvent 10ml of ethanol. then add 0.5ml of propylene glycol is used as plasticizer

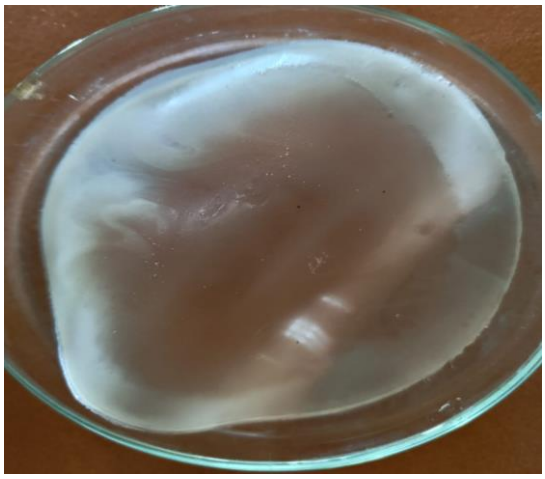
The composition of 5 films was given in the below table 1.

TABLE.1:

S.NO	FORMULATION CODE	DRUG [FAMOTIDINE]	HPMC [POLYMER]	PVP [POLYMER]	PROPYLENE GLYCOL	ETHANOL
1.	FC 1	2 mg	1 gm	1gm	0.5 ml	10 ml
2.	FC 2	2 mg	1.5 gm	0.5 gm	0.5 ml	10 ml

3.	FC 3	2 mg	0.5 gm	1.5 gm	0.5 ml	10 ml
4.	FC 4	2 mg	-	2 gm	0.5 ml	10 ml
5.	FC 5	2 mg	2 gm	-	0.5 ml	10 ml





EVALUATION TESTS OF BUCCAL FILMS [1, 2, 3,12,13,14]

Weight and thickness of films [1]

The weight and thickness of films were determined as follows:
Three films from each formulation were individually weighed using a digital balance, and the average weight of the three films was recorded.

Similarly, three films from each formulation were measured for thickness using a Digital Vernier Calliper at six different locations, and the mean thickness value was calculated.

- **Surface PH** [3]

Surface pH was determined as follows:

A solution of 2% w/v agar in isotonic phosphate buffer at pH 6.8 was prepared and poured into a Petri dish to gel at room temperature. Buccal films were then placed on the surface of the agar plate and allowed to swell completely over 2 hours. The surface pH was measured using pH indicator paper, noting the colour change after 90 seconds and comparing it to a standard colour scale.

- **Folding endurance:** [2]

Folding endurance is tested by trimming three films to the correct size and folding one film repeatedly in the same spot or up to 300 times until it breaks. When the film doesn't break after multiple folds, it demonstrates good folding endurance.

- **Swelling percentage**:[3]

Each buccal film is individually weighed (W1) and placed in a Petri plate containing phosphate buffer at pH 6.8. After collection from the Petri plate, excess surface water is removed using filter paper, and the film is weighed again (W2).
The swelling index (SI) is then calculated using the formula:

SI = [(W2 - W1)/W1] x 100

Where:
- SI stands for Swelling Index.
- W2 denotes the final weight.
- W1 is the initial weight.

➢ **Percentage moisture absorption** [1]

The percentage moisture absorption test was performed to determine the physical stability of films. 1cm diameter film placed in desiccator contain saturated solution of aluminium chloride. The humidity inside the desiccator was maintained 79.5% and the films were kept for 3 days, use the weight before and after this period to calculate the percentage moisture absorption.

It can be calculated by using formula

% moisture absorption =
[(final weight – initial weight) /initial weight] x 100

➢ **Percentage Moisture Loss**:[1]

Take 3 films of 1-cm diameter, weigh them and placing desiccator containing anhydrous calcium chloride. The films were removed, calculate the final weight of films. Now substitute the values into the formula to find out the % moisture loss.

It can be calculated by the formula,

Percentage moisture loss = (final weight – initial weight) /
Initial weight x 100

➢ **Tensile strength of films**:[2]

It is the entire mass that is required to break the film. A rectangular device which has two plates prepared by plexus glass, one is movable and the other is stationary used to calculate tensile strength.

It is calculated with formula,

TS = Breaking load / cross sectional area of the film

➢ **Drug content uniformity**:[1]

The films containing drugs divided into 3 equal pieces, each treated separately with PH 6.8 phosphate buffer solution for 24 hours, then analyse the samples using UV spectrophotometer at 268.5 nm to determine the drug content. The average of drug content from the 3 films was considered the final reading.

➢ **Invitro disintegration time:** [3,13]

In visual analysis, a pharmaceutical film can be tested in a Petri dish with 2 ml of distilled water. The dish is spun (rotate) every 10 seconds, and the time taken for the film to dissolve or break is noted as the in vitro disintegration time.

➢ **Water vapour transmission rate**:[1]

Dried vails of same diameter were filled with cacl3 and film placed. Initial weight of transmission cell (vails). They were placed in desiccator filled with kcl3 where humidity is maintained at 80 -90%. The cells were weighed at regular intervals at 18,36,54,72 hrs. Increase in weight of the film show the rate of transmission of water vapour.

It can be calculated by the formula,

$$Q = WL/S$$

Where,

Q = water vapour transmitted
W = weight of water vapour transmitted in grams
L = thickness of film in centimetres
S = surface area exposed in sq.cm

➢ **Mucoadhesive ability of films**: (12)

The mucoadhesive ability of the films was assessed using sheep buccal mucosa tissue placed on glass slides at a 60° angle. The films' adhesion to the tissue was monitored at various time intervals (15, 30, 45, 60, 75, 90, 105, and 120 minutes after application), corresponding to the permeation study timeline.

➢ **Stability studies on human saliva**:[1]

To study the stability the buccal films was placed in Petri dishes containing human saliva. The samples of human saliva were collected from 10 different individuals of age between 18 to 40 years. Changes in colour, shape, collapse and physical stability was monitored over a 6hours time period at controlled temperature of 37 degree Celsius. This method helps to access how the films hold up under the condition similar to those encountered in the oral cavity.

➢ **In vitro dissolution studies:** [2,14]

The in-vitro dissolution studies were conducted using six basket dissolution apparatus (type 2 apparatus) at 37 °C and at 50 rpm. Each film with dimension (2x3 cm) was placed on a stainless-steel basket The film sample placed on the sieve was submerged into dissolution media. Samples were withdrawn at 0, 15-, 30-, 45- and 60-min. Time intervals and filtered through 0.45µm Whatman filter paper and were analysed spectrophotometrically at 268.5 nm. To maintain the volume, an equal volume of fresh dissolution medium maintained at same temperature was added after withdrawing samples. The absorbance values were converted to concentration using standard calibration curve previously obtained by experiment.

Ph: 6.8
Buffer: Phosphate buffer (900ml)
Film size: 2×3cm
Temperature: 37±0.5°C
Speed: 50 rpm

➢ **In vivo film test on human volunteers**:[2]

The film is tested on three human volunteers. The film with dimension 1x1 cm2 containing 10 mg of famotidine were taken. Rinse the mouth thoroughly with water and apply the film to buccal mucosa for 20 min. The films were taken out and placed in the beaker containing 10 ml of solution. The volunteers are directed to rinse their

mouth with 10 ml of distilled water and the washing was added to previous solution. It is transformed into100 ml beaker, the dilutions of these solutions were taken and analysed at 268.5 nm.
Time of mucoadhesion, possible irritancy, loss of fragmentation, bad taste, dry mouth was evaluated in order to study the drug influence on the in vivo film behaviour.

- **Ex vivo permeation studies**:[1]

A study on famotidine's permeation was conducted using fresh sheep buccal mucosa in a modified diffusion cell at 37±1°C. The mucosa was placed between the donor and receptor compartments. It was attached to one end of an open-ended cylinder, which served as the donor compartment. The film was positioned to adhere to the mucous membrane. The receptor compartment was filled with IPB pH 6.8. The assembly was kept at 37°C and stirred using a magnetic stirrer. Samples were taken at specific time intervals and analysed using UV-visible spectroscopy at 268.5 nm.

- **In vitro drug release study**:[1]

In vitro release studies were conducted using a modified dissolution apparatus in pH 6.8 phosphate buffer solution at 37°C. The apparatus included a 250 ml beaker as the receptor compartment and an open-end tube as the donor tube. A magnetic stirrer assembly with an attached hot plate was used. The dissolution medium comprised 100 ml of phosphate buffer maintained at 37±1°C on a thermoregulated hot plate. The film was placed in the donor chamber, separated from the medium by a semi-permeable membrane. The donor tube was immersed in the receptor compartment containing the dissolution medium, which was stirred at a constant speed of 100 rpm using a magnetic bead. One-millilitre samples were withdrawn at predetermined intervals for all batches. After each withdrawal, an equivalent volume of phosphate buffer was added to maintain a constant volume and sink conditions. Each withdrawn sample was diluted tenfold and analysed spectrophotometrically at 268.5 nm.

- **In vivo drug release studies**:[1]

Six male New Zealand white rabbits weighing between 2 and 2.5 kg were chosen for the in vivo study. The dose of famotidine was adjusted according to the weight of each rabbit, and the optimized formulations were cut and placed on the buccal membrane using a clip. Throughout the study, a continuous infusion of dextrose solution was administered. Periodically, 1 ml of blood sample was drawn using a syringe containing 1 ml of heparin solution to prevent clotting. These blood samples were centrifuged at 2500 rpm for approximately 30 minutes. One millilitre of the supernatant was extracted, and after suitable dilution, it was analysed at 268.5 nm spectrophotometrically, following the method described for in vitro analysis.

RESULTS AND DISSCUSSION

- **Weight of the film:**

Films are assessed for their weight using digital balance and average is calculated.
Weight of film 1 – 26mg
Weight of film 2 – 23mg
Weight of film 3 – 23mg
The average weight of three films was found to be 24 mg.

- **Folding endurance:**

A film of 2x3 cm is taken and folded at same position. Cracks were not appeared even after 300 folds. It ensures the good folding endurance.
Result: crakes appear at 332 folds.

- **Mucoadhesive ability of films:**

Examined at regular time intervals for 2 hrs and examined for change in colour, shape, collapse and physical stability.

- **Percentage moisture absorption:**

The percentage moisture absorption of the film was found to be 14.28%

- **Percentage moisture loss:**

The percentage moisture loss of the film was found to be 16 %.

- **Weight uniformity:**

The patches were tested for consistent weight. All the patches show uniform weight. The average weight found was 24.

- **Drug content uniformity:**

The content of drug in each formulation is equally distributed. The chances of recovery were 85 – 90% possible.

- **Tensile strength:**

The patches which are loaded with the drug shows more tensile strength. II>I>III>IV>V. This indicates film 2 shows more tensile strength and film 5 shows less tensile strength among all the films. This happened because of hydrogen bonding between the alcohol groups of the drug and the polymer.

- **Surface PH:**

The PH of the formulation was found to be neutral to improve patient compliance and not cause any kind of irritation and allergies.

- **Drug estimation:**

The amount of drug is estimated by plotting calibration curve, films of Famotidine in phosphate buffer of PH 6.8, at wave length 268.5 nm under UV Visible spectrometer. The obeys Beer's law.

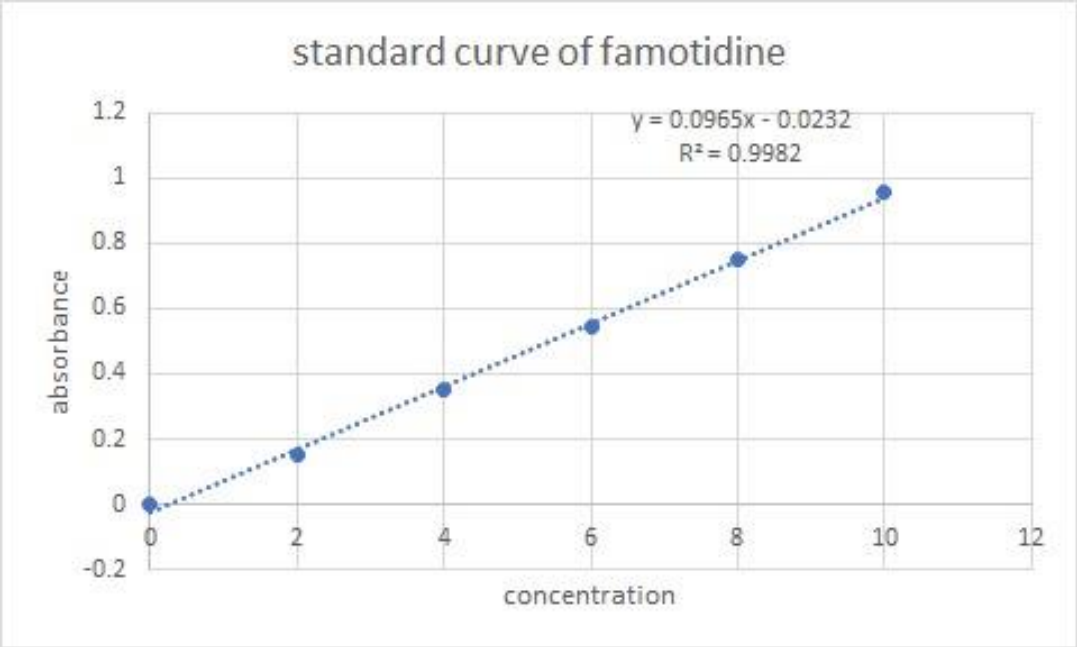
STANDARD CURVE

Standard curve of famotidine of different concentrations is obtained A concentration dependent increase in absorbance was obtained in acceptance with Beer Lambert law. The obtained curve is shown below

S.NO	CONCENTRATION (mg)	ABSORBANCE
1.	2	0.154
2.	4	0.351
3.	6	0.545
4.	8	0.752
5.	10	0.944

Discussion:

Standard plot for famotidine was plotted with r square value.



➢ **In vitro Bio adhesive test of Famotidine films:** [2,15]

The films bio adhesive nature was examined using modified balance method.

The invitro and in vivo correlation was performed to estimate the therapeutic efficacy of the formulation.

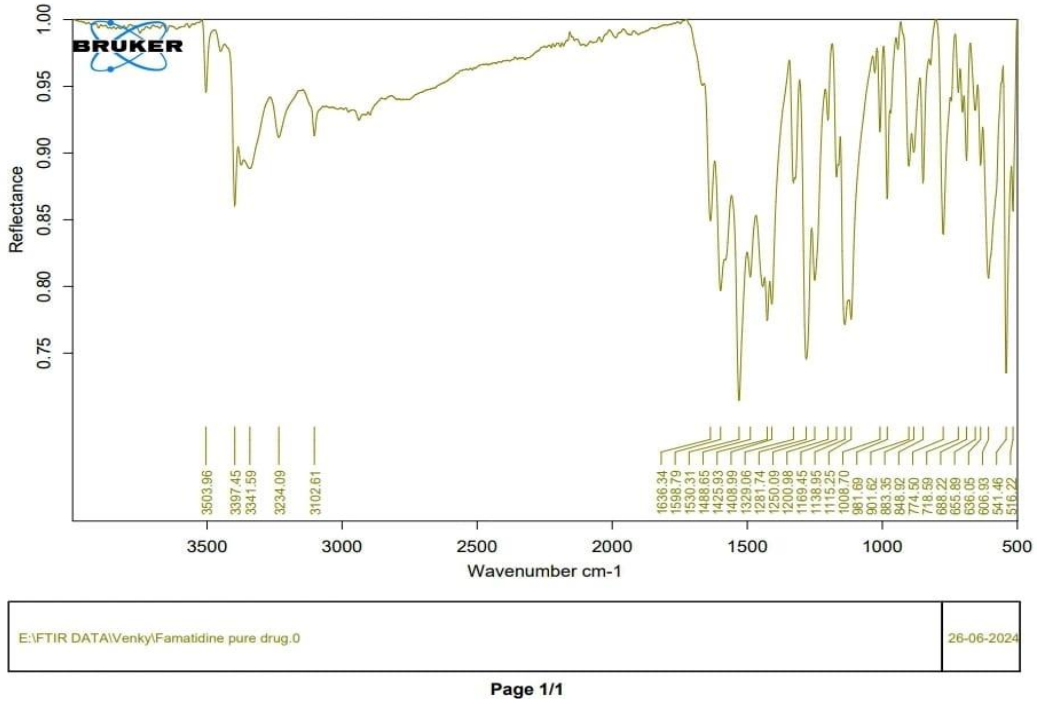
Fig 1: Bio adhesive test

The HPMC and PVP promote the bio adhesive nature resulting the film formulated by the combination of HPMC and PVP shows enhanced mucoadhesive property.

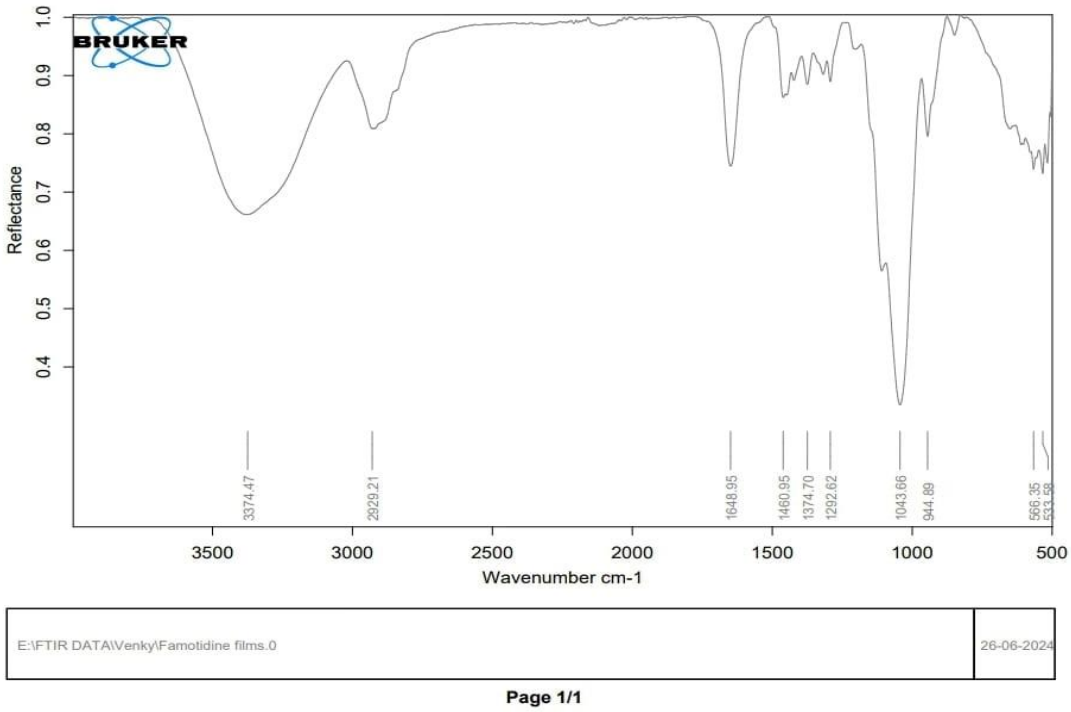
DRUG POLYMER COMPATIBILITY STUDIES

Drug polymer compatibility studies are performed by Fourier transform infrared spectroscopy (FTIR), in order to confirm there is no interaction between drug and polymer. Pure drug and all polymer used like HPMC, PVP and their combinations are analysed.

The spectral analysis of data has shown that there were greater values for optimized formulation mixture compared to pure extract. So, it was concluded that there was no interaction between drug and polymers.



FTIR of famotidine pure drug.



FTIR spectrum of famotidine and polymer film

CONCLUSION:

In the current study the Mucco adhesive buccal films of famotidine by solvent casting technique using polymer hydroxy propyl methyl cellulose and poly vinyl pyrrolidine and propylene glycol as a plasticizer are prepared and evaluated. The evaluation gives satisfactory results. The formulation shows good activity and found to be suitable for development of controlled release formulations for therapeutic use of famotidine.

In the present study, Mucco adhesive buccal films of famotidine by solvent casting method using polymer hydroxyl propyl methyl cellulose, polyvinyl pyrrolidine and Plasticizer propylene glycol are prepared and evaluated. Of all the formulations, FC 2 shows best results. Formulation FC 2 is optimized with low concentration of polymers. Formulation FC 2 shows drug release within 3min which is very less than other formulations.

The spectral analysis of data of FTIR has shown that there were greater values for optimized formulation mixture compared to pure extract. So, it was concluded that there was no interaction between drug and polymers.

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