

FABRICATION AND CHARACTERIZATION OF FAST DISSOLVING FILMS OF H₂-RECEPTOR ANTAGONIST

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ABSTRACT

Objective: The aim of the present study was to develop a fast dissolving film (FDF) of taste masked inclusion complex of Famotidine (FMT) using film forming polymer. **Method:** FDFs were prepared by solvent casting method. The developed FDFs were characterized for film thickness, disintegration time, flexibility, dissolution study. The developed FDFs of FMT were transparent, elegant, smooth and homogenous. **Results:** Physicochemical characterization of FDFs showed no interaction between the drug and film forming polymer. The drug content was found in the range of 96.05 to 102% and disintegration time was found in pharmacopoeia limit, which was less than 1 min. In vitro drug release study showed that approximately 82% drug release within 60 sec. **Conclusion:** Fast Dissolving film of famotidine is prepared that dissolve within one minute when placed on tongue. It gives fast action because it avoids the first pass metabolism. These films are preferred in geriatric and pediatric patients.

Keywords: Famotidine, oral films, solvent casting method, HPMC, carbopol

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INTRODUCTION

Fast mouth dissolving films have become popular as a new delivery system because they are easy to administer and sudden-onset of drug action is possible as the films are taken through the sublingual route. Fast-dissolving drug delivery systems have been developed as an alternative to conventional dosage form as an oral means of drug delivery in case of chronic conditions. Fast dissolving films consist of a very thin oral strip which dissolves in less than one minute when placed on the tongue. After oral administration these drugs having slow dissolution rate in gastrointestinal tract resulting low oral bioavailability due to the poor aqueous solubility [1-3]. Therefore, increasing the solubility or dissolution rate of class II drugs can improve the oral bioavailability [4-6].

Famotidine (FMT) is H₂-receptor antagonist, potent histamine having low oral bioavailability and bitter taste. FMT is used for the treatment of ulcers like peptic ulcer and to treat, prevent heartburn due to acid indigestion and sour stomach caused by eating or drinking certain foods or drinks [7-8]. Some of the patients groups particularly pediatrics and elderly patients may have swallowing problems of the conventional solid dosage form such as tablets and capsules. This leads to the prolonged duration of action and patient's non-compliance, which can be

solved through the development of orally disintegrating dosage forms that disintegrate in the saliva and are swallowed without water [9-12]. Famotidine is used to treat ulcers of the stomach and intestines and to prevent intestinal ulcers from coming back after they have healed. This medication is also used to treat certain stomach and throat (esophagus) problems (such as erosive esophagitis, gastroesophageal reflux disease-GERD, Zollinger-Ellison syndrome). It works by decreasing the amount of acid your stomach makes. It relieves symptoms such as cough that doesn't go away, stomach pain, heartburn, and difficulty swallowing. Famotidine belongs to a class of drugs known as H₂ blockers [13].

The main objective of this work was to develop fast dissolving film of taste masked inclusion complex of Famotidine using chitosan (CH), biodegradable, film forming polymer. Chitosan is the best known natural polymer used for its versatile applications in pharmaceutical industry. Along with general applications as binder, diluents, wetting agent, disintegrant, preparation of hydrogels, and improvement of dissolution of poorly soluble drug substances. Chitosan has been used to develop fast mouth dissolving film due to its superdisintegrant property.

MATERIAL AND METHOD

Famotidine, Carbopol, Ethanol, HPMC, Purified water, Saccharine, Propylene Glycol, Polyvinyl acetate

Fabrication of Drug Free Films

The films were prepared by the method of solvent casting technique employing 'O' shape ring placed on a glass surface as substrate by using different polymers like Hydroxypropyl methylcellulose-15 cP, and polyethylene glycol. The calculated quantities of polymers were dispersed in distilled water. The polymeric solutions were levigated with 30 % w/w

propylene glycol which served the purpose of plasticizer as well as penetration enhancer. The solution was mixed occasionally to get semisolid consistency. Then the solution was subjected to sonication in a bath sonicator to remove the air bubbles. Then this were casted on a glass surface employing 'O' shape ring having 3.6 cm in diameter is covered with funnel to controlling the evaporation of solvent and allowed to dry at room temperature overnight. The dried films were separated. Then the formulations were stored in desiccators until further use.

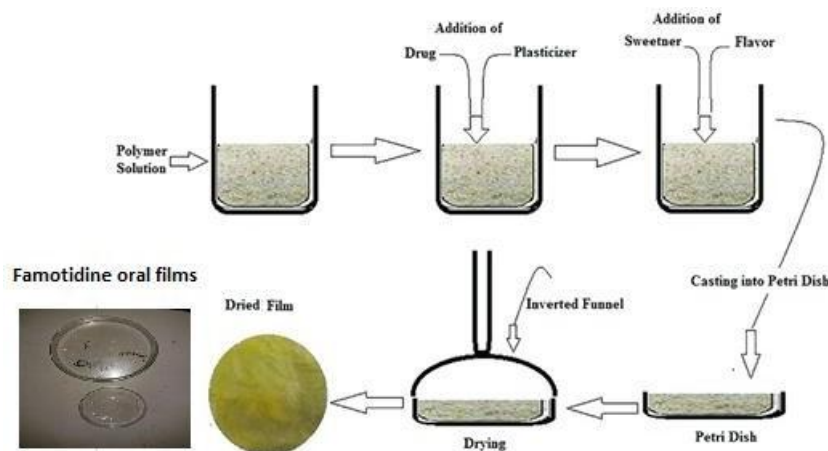


Figure 1: Flow chart for preparation of famotidine oral films.

Fabrication of Famotidine Films

The films were prepared by the method of solvent casting technique employing 'O' shape ring placed on a glass surface as substrate by using different polymers like Hydroxypropyl methylcellulose-15 cps(HPMC) and The calculated quantities of polymers were dispersed in distilled water. An accurately weighed 20 mg Famotidine was incorporated in polymeric solutions after levigation with 30 % w/w propylene glycol which served the purpose of plasticizer as well as penetration enhancer. The solution was mixed occasionally to get semisolid consistency. Then the solution was subjected to sonication in a bath sonicator to remove the air bubbles Then this were casted on a glass surface employing 'O' shape ring having 3.6 cm in diameter is covered with funnel to control the evaporation of solvent and allowed to dry at room temperature overnight. Then the formulations were stored in desiccators until further use.

Formulation F1 is prepared by using PVA but film is not found because film cannot dispatch.

In formulation F2 we used ethanol as a solvent but it will evaporate and no film is prepared.

In formulation F3a, F3b, F3c we used following concentration of chemicals as shown in table:

Table 1: Formulation composition of famotidine films.

Ingredients	FF1	FF2	FF3
Famotidine (mg)	20	20	20
HPMC 15K (mg)	200	180	160
Ethanol (70% v/v (ml)	9.5	9.5	9.5
Polyethylene glycol (ml)	0.5	0.5	0.5
Carbopol	...	20	40
Total weight (mg)	250	250	250

Physico-chemical Evaluations

Surface pH

Fast dissolving films were left to swell for 2 h on the surface of an agar plate, prepared by dissolving 2 % (w/v) agar in warmed isotonic phosphate buffer of pH 6.8 under stirring and then pouring the solution into a Petri dish till gelling at room temperature. The surface pH was measured by means of a pH paper placed on the surface of the swollen patch [14].

Percentage Moisture Absorption

The percent moisture absorption test was carried out to check the physical stability of the oral films at high humid conditions. In the present study, the moisture absorption capacity of the films was determined as

follows. Three 1cm diameter films were cut out and weighed accurately then the films were placed in desiccators containing saturated solution of aluminium chloride, keeping the humidity inside the desiccators at 79.5 %. After 3 days the films were removed, weighed and percentage moisture absorption was calculated. Average percentage moisture absorption of three films was found [14].

$$\text{PMA} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Percentage Moisture Loss

This test was also carried to check the integrity of films at dry condition. Three 1cm diameter films was cut out and weighed accurately and kept in desiccators containing fused anhydrous calcium chloride. After 72 hours the films were removed and weighed. Average percentage moisture loss of three films was found out [15].

$$\text{Percentage Moisture Loss} = \frac{[\text{Initial weight} - \text{Final weight}]/\text{initial weight}}{100} \times 100$$

Swelling Percentage

Drug loaded films were placed in a thoroughly cleaned Petri dish having 50 ml of pH 6.8 phosphate buffer. An increase in the weight of the patch was noted in 15 min intervals for 60 min and the weight was calculated [16].

The swelling percentage was calculated by using the following formula.

$$\% S = (X_t - X_0)/X_0$$

Where,

% S = swelling percentage

X_t = the weight of swollen film after time t,

X_0 = weight of film at zero time.

Water Vapor Transmission Rate

For this study vials of equal diameter were used as transmission cells. These cells were washed thoroughly and dried in an oven. About 1 g of calcium chloride was taken in the cell and the polymeric films measuring 1 cm² area were fixed over the brim with the help of an adhesive. The cells were weighed accurately and initial weight was recorded and then kept in a closed desiccators containing saturated solution of potassium chloride. The humidity inside the

Desiccators were found in between 80 – 90 % RH. The cells were taken out and weighed after 18, 36, 54 and 72 hrs. From increase in weights the amount of water vapor transmitted and the rate at which water vapor transmitted were calculated by using the following formula [17].

$$WVT = WL/S$$

Where,

W is water vapor transmitted in mg, L is thickness of the film in mm, and S is exposed surface area in cm².

Film Thickness and Weight

The thickness of each film was measured by using a digital vernier caliper at six different positions of the film and the average thickness was calculated [18]. The weight of three films was taken and the weight variation was calculated on analytical balance.

Folding Endurance

Folding endurance of the film was determined by repeatedly folding one patch at the same place till it broke or folded up to 300 times manually, which was considered satisfactory to reveal good film properties. The number of times of film could be folded at the same place without breaking gave the value of the folding endurance [10, 11].

Drug Content Estimation

A film was cut into three pieces of equal diameter were taken in separate 100 ml of pH 6.8 phosphate buffer was added and continuously stirred for 24 h. The solutions were filtered, suitably diluted and analyzed at 289 nm in a UV Spectrophotometer.

In-Vitro Drug Release Studies

The in-vitro release studies were performed in phosphate buffer solution (pH 6.8, 100 ml) at 37 °C using a modified dissolution apparatus. The modified dissolution apparatus consisted of a 250 ml beaker as a receptor compartment and an open end tube as a donor tube. The magnetic stirrer assembly with an attached hot plate was adopted for the study. The dissolution medium consisted of 100 ml of phosphate buffer (pH 6.8) maintained at 37 ± 1 °C by means of a thermo-regulated hot plate. Film was placed into the donor chamber of the assembly separated from the medium by a semi-permeable membrane. The donor tube was then dipped into the receptor compartment containing dissolution medium, which was maintained at 37 ± 1 °C and stirred at a constant speed of 100 rpm using a magnetic bead. One milliliter samples were withdrawn at predetermined time intervals for all the batches. For each sample withdrawn, an equivalent volume of phosphate buffer was replaced to the dissolution medium to maintain constant volume and sink condition. A ten-fold dilution of each of the withdrawn sample was made and the diluted solutions were thereafter analyzed spectrophotometrically at 289 nm.

Disintegration Time

The films were placed in petri dish along with 10ml of water and the time taken for them to disintegrate was notes using a stopwatch [13].

RESULTS AND DISCUSSION

The thickness of all the films was within acceptable limits. The surface pH of the films was within acceptable limits. The pH of the films needs to be between 6 and 8 so that it may not cause any

Table 2: Physicochemical properties of famotidine oral films.

Parameters/Formulation	FF1	FF2	FF3
Surface pH	6.71±0.05	6.73±0.05	6.80±0.02
PMA	5.21±0.07	7.32±0.09	9.24±0.09
PML	5.97±0.12	5.14±0.72	4.74±0.1
Swelling index (%)	69.4±1.04	99.67±0.69	118.4±0.72
Thickness (mm)	0.24±0.01	0.47±0.01	0.62±0.01
Weight of films (mg)	180.9±1.55	169.18±0.9	171.53±.81
Folding endurance (times)	301±2.0	303±3.0	300±1.0
Drug content (mg)	19.7	18.9	19.3

corrosive harm to the oral mucosa. The contact angle was within a normal range as well. The results of swelling index, PMA, drug content and PML, weight of film, and folding endurance are shown in table 2. Cumulative drug percent release is shown in Fig 2. The swelling behavior of the polymer is reported to be crucial for its bioadhesive character. The adhesion occurs shortly after swelling but the bond formed is not very strong. The adhesion increases with the degree of hydration till the point of disentanglement at the polymer tissue surface, which leads to abrupt drop in adhesive strength due to overhydration. The formulation FF3 showed high swelling percentage (118±0.72) which is due to the presence of higher concentration of CP [19].

Cellulose derivatives are known for their good film forming properties and have an excellent acceptability [20]. Cellulose derivatives namely HPMC E5 and CMC were used as main film formers. Various trials were done to formulate the FDF. Films of HPMC E5 and CMC were transparent in appearance with excellent film forming capacity. pH of FF3 formulations decreases because of addition of carbopol. Carbopol is basically acrylic acid (brand name is carbomer). By decreasing the amount of HPMC the PMA of FF3 formulations increases because of carbopol addition. Carbopol is better moisture absorbent than HPMC. By decreasing the amount of HPMC the PML of FF3 formulations decreases because of carbopol addition. It shows that at which rate carbopol absorb moisture at the same rate it loses water. Carbopol is readily swellable so by increasing the concentration of it in FF3 formulations, (% S) and thickness increases [21].

Weight of carbopol is very less than HPMC, so FF3 formulations have less molecular weight. As we reduce the amount of HPMC used, the folding endurance of films does not vary significantly. Which shows elasticity of films depends upon plasticizer used not on polymer. The folding endurance was found to be greater than 300 times in the case of all the formulations. This makes the system acceptable for movement of mouth, indicating good strength and elasticity.

Folding endurance test results indicate that the films would maintain the integrity with buccal mucosa when applied. CP, being an anionic polymer, gives the highest buccoadhesive force. The buccoadhesive strength exhibited by famotidine oral films was satisfactory for maintaining them in oral cavity. The combination of HPMC and CP shows good adhesion. Upon addition of PVP, the buccoadhesive strength increases which may be due to hydrogen bond formation and Vander Waals forces. CP is present in an ionized state, and as a result, the polymeric network gets loosened comparatively, attributing for the higher drug release. The addition of PVP decreases the famotidine release which may be due to enhancement in swelling of the polymer, which in turn increases the barrier effect and decreases the drug release, thereby controlling the drug release [19]. Variations in drug contents were negligible. Results showed that drug content was released within appropriate limits. The disintegration time of the films fell within reasonable precision. Dissolution is the most important parameter for orally fast dissolving films. All the formulations of famotidine films were evaluated for various physicochemical

parameters and they were found to within limits. Among all the formulations, FF3 formulation showed highest % of drug release i.e. 99.6% in 60 seconds highest among all formulation.

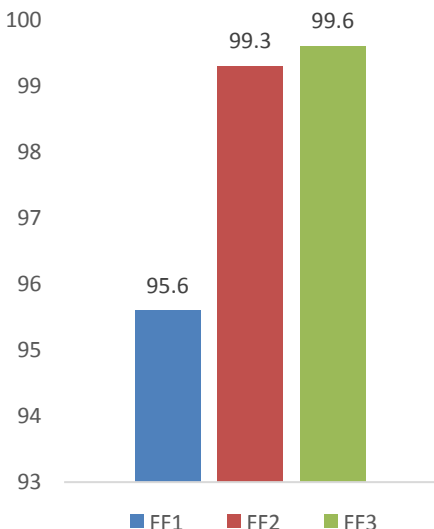


Figure 2: Comparative in-vitro drug release of famotidine oral films percentage in seconds.

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CONCLUSION

The famotidine oral films were prepared by the method of solvent casting technique employing O-shape ring placed on a glass surface as substrate by using different polymers such as Hydroxypropyl methylcellulose-15 cP, and poly ethylene glycol glycol. Distilled water is used as the solvent. PEG serves as the plasticizer as well as penetration enhancer. The prepared famotidine films were characterized based upon their physico-chemical characteristics like surface pH swelling percentage, thickness, weight variation, drug content, percentage moisture absorption, percentage moisture loss, Folding endurance, in-vitro release studies. Based on the results of evaluation tests, the formulation coded “F3” was concluded as best formulation. In vitro drug released study showed that approximately 99.6 percent drug released within 1 min in comparison to the pure drug. From the study we can conclude that FDFs formulation could be an alternative approach for the delivery of various drugs for the pediatrics as well as elderly patients which having swallowing problems.

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