

PREPARATION OF MUCOADHESIVE TABLETS OF FAMOTIDINE BY WET GRANULATION METHOD AND ITS *IN-VITRO* TESTING

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ABSTRACT

Objective: Famotidine is a histamin H₂-receptor antagonist. The aim and objective of the present work is to formulate and evaluate mucoadhesive tablets of famotidine. It is also focused on the selection of mucoadhesive polymer & its activity in various combinations & ratios. The poor bioavailability & shorter half-life suffice the development of controlled release mucoadhesive formulation. **Method:** Mucoadhesive tablets each containing 20mg of famotidine were prepared by conventional wet granulation method employing as mucoadhesive materials. A batch of 50 tablets was prepared, in each case a blend of 1 gm of famotidine with different polymers addition in different strengths with required 40mg lactose as diluent achieved after titration which were then granulated along with a solvent blend of water and ethyl alcohol. **Results:** The flow properties of all five batches were in between fair and passable. Hardness of tablets ranged from 6.9-8.2 kg/cm² and the percentage friability was between 0.25-0.79 %. The drug content uniformity in the mucoadhesive tablets was 96.49-104.81%. The surface pH study was within the range from 6.7-7.4. From all formulations, over 20% of the famotidine was release within first hour of dissolution study. In the present study the formulation FT04 (tragacanth & HPMC) has shown cumulative percent drug release of about 80.762% in 12 h. **Conclusion:** From the results we concluded that formulation containing famotidine with HPMC & tragacanth has given better drug release property than the other four formulations & the wash-off test has shown that this formulation (FT04) has better mucoadhesive property.

Keywords: Famotidine, HPMC, Tragacanth, Mucoadhesive.

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INTRODUCTION

Famotidine is "N'(aminosulfonyl)-3-[[[2(di-amino-methylene)amino]-4thiazolyl] methyl] thio] propan imidamide. The empirical formula of famotidine is C₈H₁₅N₇O₂S₃. Famotidine is a histamine H₂-receptor antagonist. Famotidine (FM) is indicated for active and maintenance therapy of several types of ulcers and hypersecretory conditions [1].

Famotidine, a new, potent, long-acting histamine H₂-receptor antagonist was compared with cimetidine and ranitidine in 9 patients with Zollinger Ellison syndrome. The mean minimum daily requirement of famotidine to control gastric acid hypersecretion was 0.24 g (range 0.08–0.48 g) compared with 2.1 g (range 0.6–3.6 g) for ranitidine and 7.8 g (range 1.2–13.2 g) for cimetidine.

Equally potent doses of the three drugs had similar onsets of action, but the duration of action of famotidine was 30% longer than the duration of

action of either ranitidine or cimetidine (p < 0.05). Eight patients were treated for up to 9 mo. (mean 6 mo.) with good control of gastric acid hypersecretion and with no evidence of biochemical or hematologic toxicity.

These studies demonstrate that famotidine is nine times more potent than ranitidine and 32 times more potent than cimetidine, has a longer duration of action than ranitidine or cimetidine, and is both safe and effective in the long-term therapy of Zollinger Ellison syndrome.

The aim and objective of the present work is to formulate and evaluate famotidine tablets. It is also focused on the selection of mucoadhesive polymers and its activity in various combinations and ratios [2]. Famotidine is rapidly but incompletely absorbed with low bioavailability from the stomach. The poor bioavailability and short biological half-life suffice

the development of controlled release mucoadhesive formulation. It is focused to formulate famotidine by addition of different polymers in different ratios and then to perform the in-vitro studies to evaluate the formulation [3].

MATERIALS AND CHEMICALS REQUIRED

The materials and chemicals employed in our project includes Famotidine, HPMC, Microcrystalline cellulose, Methyl cellulose, Gum tragacanth, PEG 600, Lactose, Magnesium stearate, Gum acacia, Talc, Sodium alginate, Ethanol, Distilled water.

Preparation of Granules

Five different type of granules were prepared by addition of different granules in different ratio by wet granulation method. The work done is describe below in the **Table 1**:

Take a neat and clean apparatus and weight required quantity of material carefully. Mucoadhesive tablets each containing 20 mg of Famotidine were prepared

by conventional wet granulation method employing as mucoadhesive materials. A batch of 50 tablets was prepared in each case a blend of 1 gm of famotidine was taken with 40 mg of HPMC in FT01, 20 mg sodium alginate and 20 mg gum acacia in case of FT02, 40 mg sodium alginate, 20 mg HPMC in FT03, 20 mg gum tragacanthin, 40 mg HPMC in case of FT04, 20 mg HPMC, 20 mg PEG 600 in FT05 and required 40 mg lactose as diluent achieved after titration which were then granulated along with a solvent blend of water and ethyl alcohol (1:1) [4].

Then the solvent is added drop wise with continuous stirring until the wet mass is formed. Then the wet masses were passed through 12 mesh sieve and wet granules were dried at 60° C for 4 hours. The dried granules (20 mesh) after blending with talc (0.5gm) and magnesium stearate (0.5 gm) in blender for 5 mins were compressed into 50 tablets by using a single tablet punch machine [5].

Table 1: Combination of ingredients for formulation of different mucoadhesive tablets.

Ingredients (mg/tab)	Formulations				
	FT01	FT02	FT03	FT04	FT05
Famotidine	20	20	20	20	20
HPMC	40	-	20	40	20
Sodium alginate	-	20	40	-	-
Tragacanthin	-	-	-	20	-
PEG 600	-	-	-	-	20
Gum acacia	-	20	-	-	-
Lactose	40	40	40	40	40
Talc	10	10	10	10	10
Magnesium stearate	10	10	10	10	10

Punching of Tablet

Apparatus used for punching the granules to form the tablet is single tablet punch machine. Firstly, the granules were carefully weight on the weighing balance then the dye of the machine was filled with the granules and compression forces applied. After which the Tablet punched was ejected from the dye. This step is repeated for every tablet from the batch FT01, FT02 FT03, FT04 and FT05 respectively. Total 250 tablets were punched, 50 from each batch and then these tablets were used for the *in-vitro* testing [6]. After the in vitro testing form every batch 10 tablet were packed in the blisters and are then packed by using an aluminium foil.

Evaluation and Testing

The physical evaluation tests for the mucoadhesive tablets of all the formulations were performed and mean values were calculated.

Hardness

It is the load require to crush the tablet when place on its edges [1]. Five tablets were randomly selected

from every batch and crushing strength of each tablet was measured using Monsanto hardness tester. The mean hardness of five tablets was determined and expressed in Kg/cm² [7].

Weight Variation Test

Weight variation analysis was done by weighing 20 tablets individually, the average weight was calculated and % variation of each tablet from the average weight of tablets was calculated. The test was carried out according to Indian Pharmacopoeia, 20 tablets were randomly selected form each batch accordingly, weighed together and individually for the determination of uniformity of weight of tablets. The mean and percent deviations were determined. Formulated tablets comply with the test if not more than two of the individual weights deviate from the average weight by more than the percentage and none deviate more than twice the percentage.

Friability Test

It is performed to check whether the tablets we made can withstand any kind of fracture or breakage during

packing or transportation.

- 1) Take 5 tablets from each batch i.e., FT01, FT02, FT03, FT04 & FT05, get them rid of the dust using the compressed air, weighed them to put in a friability tester. (Figure 3).
- 2) Turn on the apparatus by pressing the knob “mains” to set the rotation speed to 25 rpm.
- 3) Start the rotation of the device by pressing “start/stop” button.
- 4) End the rotation after 4 minutes by re-pressing “start/stop” button.
- 5) Take out the tablets, get them rid of the dust and weight them.
- 6) Calculate the relative weight loss of the tablets and discuss the compliance to the requirement for the tablet friability test.
- 7) Discuss the differences between the formulations [8, 9].

Disintegration Test

1. Start the disintegration test on 6 tablets from every batch accordingly.
2. Into the beaker of 1000 ml put water of 37 ± 2 °C. Fix the basket to the disintegration tester and place the beaker with water.
3. Adjust the water level to achieve the bottom of basket being 15-20 mm below the water level at the top dead center movement of the basket.
4. Set the motor rotation speed to the minimal value (30 rpm).
5. Insert the tablet, turn on the motor and begin to measure the disintegration time.
6. Observe visually the course of the test.
7. The end of the test is the time when there is no residue of the tablet left in the basket.

Drug Content Uniformity

The tablets were kept in 100 ml volumetric flask containing phosphate buffer pH 4.5 for 24 h. When tablets were completely dissolved the solution was centrifuged. After centrifuged the supernatant was collected. Absorbance was measured spectrophotometrically at 267 nm. Dilution was made using phosphate buffer (pH 4.5) as per requirement.

Dissolution Test

The *in vitro* drug release study was performed using USP dissolution rate test apparatus (paddle type; 50 rpm). Dissolution study was carried out for 12 h. Phosphate buffer (pH 4.5; 900 ml) was used as dissolution media. Samples of each 5 ml were withdrawn after every 1 h for a period of 12 h. Volume in dissolution vessel was kept constant by equal replacement with fresh media. The samples were collected in test tubes after filtration through Watt Mann filter paper. The amount of the drug in the aliquots was quantified by taking the absorbance of the sample at 267 nm spectrophotometrically,

using phosphate buffer pH 4.5 (dissolution media) as the blank [10, 11].

Surface pH

The surface pH was determined to investigate the possible *in vivo* side effects of the formulation. An acidic or alkaline formulation causes irritation of the mucosal membrane and hence, this is an important parameter in developing a mucoadhesive dosage form.

A combined glass electrode was used for determination of surface pH. The tablets were kept in contact with 5 ml distilled water pH 6.5 ± 0.5 for 2 h in 10 ml beakers. The tablets swell up and pH was noted by bringing the electrode near the surface of the formulation after equilibrating for 1 min [12].

Thickness Test

Thickness of each tablet was measured in mm using a digital Vernier Calliper. The mean and standard deviation values were calculated and reported [5, 9].

RESULTS AND DISCUSSION

The prepared mucoadhesive tablets were evaluated for various physical parameters such as weight variation, hardness, friability and drug content. All the batches were produced under conditions to avoiding processing variables.

Hardness of Tablets

Hardness of tablets ranged from 6.9-8.2 kg/cm² is within limit of IP. The values of hardness test indicate good handling property of prepared mucoadhesive tablets.

Weight Variation Test

The weight variation calculated for all of five batches of Famotidine 20 mg were within the range of Indian pharmacopeia [13]. The values of hardness test and percentage friability indicates good handling property of prepared mucoadhesive tablets.

Friability Test

The percentage loss in weight calculated was within limit of IP. The values of hardness test and percentage friability indicates good handling property of prepared mucoadhesive tablets.

Disintegration Test

The test performed were within the range of standard criteria.

Drug Content Uniformity

The drug content uniformity in the mucoadhesive tablets was within the range from 96.49 -104.81% as shown in table 2.

Surface pH

The surface pH study in the mucoadhesive tablets was within the range from 6.7-7.4 as shown in table:

Dissolution Test

From all formulations, over 20% of the famotidine was release within the first hour of dissolution study. In the present study the formulation FT04 (tragacanth

& HPMC) has shown cumulative percent drug release of about 80.762% in 12 h.

Organoleptic Testing

The tablets prepared were white in colour as there is no addition of colourant in them, circular in shape, small sized of average equal thickness and approximately odourless or having slight odour [14].

Adhesiveness

Mucoadhesion, an interfacial phenomenon, is based on two materials, one of which is mucus layer of mucosal tissue to which the drug is held together by means of interfacial forces for prolonged period. Control release system ensures localization of drug in a site to improve and increase the bioavailability [15]. The contact time is also enhanced due to interaction between polymers and mucus lining of tissue for

sustained action. Advance polymer systems in controlled delivery systems maintain the release rate as well as the concentration in the biological system by increasing its localization and avoiding first pass metabolism. Mucoadhesion as a means of influencing the duration of contact of medicinal formulations with mucous membranes immediately became a subject of interest to technologists.

Drug Release

From all formulations, over 20% of the famotidine was release within the first hour of dissolution study. In the present study the formulation FT04 (tragacanthin& HPMC) has shown cumulative percent drug release of about 80.762% in 7.7 h.

Table 2: Evaluation parameters of mucoadhesive formulations.

Tests done	FT01	FT02	FT03	FT04	FT05
Hardness (kg/cm ²)	7.1	7	8.2	8.1	8
Weight variation	Within the range of indian pharmacopeia (10 % deviation)				
%age loss in weight	0.46%	0.45%	0.61%	0.41%	0.52%
Disintegration time(min)	24	24	21	28	22
%age Drug content	98.12	98.23	101.5	102.3	101.54
Surface pH	7.2	7.3	6.1	7.4	7.3
Average detachment time (min)	401	422	379	465	398

CONCLUSION

The prepared Mucoadhesive tablets were evaluated for various physical parameters such as weight variation, hardness, friability and drug content. All the batches were produced under conditions to avoiding processing variables. The values of hardness

test and percentage friability indicates good handling property of prepared Mucoadhesive tablets. The drug content uniformity in the Mucoadhesive tablets was within the range

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