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FORMULATION AND EVALUATION OF MOUTH DISINTEGRATING TABLETS OF FAMOTIDINE BY USING *HIBISCUS ROSA - SINENSIS* MUCILAGE AND TREATED AGAR

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ABSTRACT

Mouth disintegrating tablets are those tablets which disintegrate/dissolve in the mouth with in the fraction of seconds. These tablets are helpful for all age groups especially geriatric and paediatric patients. This type of dosage forms helps a lot to dissolve in the mouth without the need of water and also increase the bioavailability of the drugs rapidly. Newer methods are also applied in preparing the MDT's.

Purpose of the present work is to formulate the mouth dissolving tablets of Famotidine by using natural polymers to achieve quick onset of action, to increase absorption and helps to obtain maximum bioavailability. Famotidine dissolving tablets were prepared with mucilage of *Hibiscus Rosa - sinensis Linn* and treated agar. Pre-compression parameters like angle of repose and post-compression parameters like wetting time, water absorption ratio, *in-vitro* disintegration and *in-vitro* dispersion time were studied. The hardness, friability and drug content of all the formulations were found to be within the limits. The best formulations FHR4 and FTG3 have shown good disintegration time, hardness and friability. The best promising formulations were also found to be stable. This natural polymers helps a lot in economic way to achieve rapid disintegration and rapid onset of drug action in the body.

KEYWORDS: Mouth disintegrating tablets, Water absorption ratio, Treated agar,Famotidine.

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INTRODUCTION

Formulation of a convenient dosage form for administration, by considering swallowing difficulty and poor patient compliance, leads to development of mouth disintegrating tablets. This are also called as mouth dissolving, rapidly disintegrating, and fast melt system. This disintegrates in the mouth in seconds without chewing and the need of water which is advantageous mainly for pediatrics, geriatrics and patients having difficulty in swallowing tablets and capsules. Conventional preparation methods are spray drying, freeze drying, direct compression, Molding, and sublimation while new technologies have been developed for the production of mouth disintegrating tablets.

Fast dissolving tablets are dosage form, which disintegrate in patient's mouth within a few seconds without the need of water, or chewing, providing best remedy for the patient suffering from dysphasia. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down the stomach4. In such cases the bioavailability is greater than those observed for conventional dosage form. The advantages of mouth dissolving dosage form are increasingly being recognized in both industry and academia[1-4].

Mucilage is glutinous substance which mainly consists of polysaccharides, proteins and uranides Mucilage of the Hibiscus Linn and treated Agar used in this present work. Thus agar is modified to treated agar by treating with water for one day. Naturally the demand of these substances is increasing and new sources are tapped. India due to geographical and environmental positioning has traditionally been a good source for such products[5-6].

Famotidine is a histamine H2-receptor antagonist. It is widely prescribed in gastric ulcers, duodenal ulcers, Zollinger- Ellison syndrome and gastroesophageal reflux disease. It is a popular and selective H2 receptor antagonist with a limited aqueous solubility of the 0.1%w/v at 20°C, it causes rise to difficulties in the development of dosage forms[7].

Now a days, the natural polymers are also playing a vital role in the drug delivery systems which are showing the less side effects, less cost effective with wide spread availability in all the natural regions around the world. In this study, natural substances like mucilage of *Hibiscus Rosa sinensis Linn* and treated agar were used in the preparation of mouth disintegrating tablets by direct compression method.

MATERIAL AND METHOD

Famotidine was received as a gift sample from Fourrts India Pvt. Ltd. Chennai. India. Avicel PH 102 was supplied by Dr. Reddy Laboratories. Mumbai. *Hibiscus Rosa- sinensis Linn* was obtained from the local place. Agar (dried extract of *Gelidium Sp*. Family Rhodophyceace) from Loba fine chemie, Mumbai. L-HPC, dioxide and Magnesium stearate obtained from Cipla Ltd, Mumbai. All the ingredients received were of pharmaceutical grade and were used as received. Other materials and solvents used were of analytical grade.

Preparation of Mucilage

The fresh leaves of *Hibiscus rosa-sinensis Linn* were authenticated from the Ayurvedic medical college Botanist and specimen was kept in the college and specimen number is HSK/2010/010. The fresh leaves of *Hibiscus rosa-sinensis Linn* were collected, washed with water to remove dirt and debris, and dried. The powdered leaves were soaked in water for 5–6 h, boiled for 30 min, and kept aside for 1 h for complete release of the mucilage into water. The material was squeezed from an eight fold muslin cloth bag to remove the marc from the solution. Acetone was added to the filtrate to precipitate the mucilage in a quantity of three times the volume of the total filtrate. The mucilage was separated, dried in an oven at a temperature < 50 °C, collected, dried powdered, passed through a sieve (number 80), and stored for further use in desiccators[8].

Preparation of Treated Agar

Agar powder (dried extract form *Gelidium Sp*. Family Rhodophyceace) were authenticated from the Ayurvedic medical college Botanist and specimen was kept in the college. The specimen number is HSK/2010/011.. Agar Suitable quantity of Agar powder (5-10g) weighed and added in distilled water (100ml). Agitation was done continuously by a stirrer for one day to swell. The swollen contents were

dried on a tray for 3 days at room temperature. The dried powders were grinded by mortor and pestle. Then grinded powder was passed through sieve no.100. [9]

Preparation of Mouth Disintegrating Tablets of Famotidine

First, the Famotidine drug is mixed with the suitable quantity (as mentioned in **table 1**) of Treated agar and *Hibiscus rosa-sinensis Linn* mucilage and then all the ingredients mixed in the increased order. Lastly powder blend were mixed and lubricated with magnesium stearate and compressed using single punch tablet machine the mean weight and diameter of the tablets were 200mg and 7 mm, respectively.

EVALUATION OF POWDER

Precompression Parameters

Angle of repose

Angle of repose was determined using funnel method4. The blend was poured through funnel that can be raised vertically until a maximum cone height (h) was obtained. Radius of the heap (r) was measured and angle of repose was calculated using the formula[10]

$$\theta = \tan^{-1} \frac{h}{r}$$

Where, θ is the angle of repose, h is height of pile; r is radius of the base of pile.

Bulk density

Apparent bulk density was determined by pouring presieved drug excipient blend into a graduated cylinder and measuring the volume and weight "as it is" [10]. It is expressed in g/ml and is given by

$$\text{LBD (Loose Bulk Density)} = \frac{\text{Mass of Powder}}{\text{Volume of Packing}}$$

Tapped density

It was determined by placing a graduated cylinder, containing a known mass of drug- excipient blend, on mechanical tapping apparatus. The tapped volume was measured by tapping the powder to constant volume.[10] It is expressed in g/ml and is given by

$$\text{TBD (Tapped Bulk Density)} = \frac{\text{Mass of Powder}}{\text{Tapped Volume of Packing}}$$

Powder flow properties

The flow properties were determined by

Carr's Index (I)

It is expressed in percentage and is expressed by

$$\text{Carr's Index \%} = \frac{\text{TBD} - \text{LBD}}{\text{TBD}} \times 100$$

Evaluation of Tablets

All formulation tablets were evaluated for the following post compression parameters

General appearance

Tablets of different formulations were randomly selected and organoleptic properties such as color, odor, taste, shape, were evaluated.

Thickness

Thickness of tablets was determined using Vernier caliper. Five tablets from each batch were used, and an average value was calculated.

Hardness

The hardness was determined by using the Monsanto hardness tester

Friability

The friability was measured using a Friability tester (Electro Lab). Ten tablets were weighed, rotated at 25 rpm for 4 minutes. Tablets were reweighed after removal of fines (dedusted) and the percentage of weight loss was calculated.

Uniformity of weight

Twenty tablets were randomly selected from each formulation, individually weighed, the average weight and standard deviation was calculated.

Drug content

Twenty tablets from each batch were powdered and weighed accurately equivalent to 100 mg of Famotidine. The drug content was determined using the standard calibration curve. The mean percent drug content was calculated as an average of three determinations. Weighed quantity of powder samples were diluted suitably and analyzed at 265nm for cumulative drug release using Elico-159 UV-Visible spectrophotometer.

***In vitro* dispersion test**

This test is performed to ensure disintegration of tablets in the salivary fluid, if it is to be used as an mouth disintegrating/dissolving tablet. *In vitro* dispersion time was measured by dropping a tablet in a measuring cylinder containing ml of simulated salivary fluid of pH 6.8. Five tablets from each formulation were randomly selected and *in vitro* dispersion time was performed.

***In vitro* Disintegration test**

The disintegration time was measured using disintegration test apparatus. One tablet was placed in each tube of the basket. The basket with the bottom surface made of a stainless-steel screen (mesh no. 10) was immersed in water bath at 37 ± 2°C. The time required for complete disintegration of the tablet in each tube was determined using a stop watch. To be complied with the pharmacopoeial standards, dispersible tablets must disintegrate within 3 min when examined by the disintegration test for tablets.

Wetting time and water absorption ratio

A piece of tissue paper (12cmx10.75cm) folded twice was placed in a Petri dish (Internal Diameter=9cm) containing 6 ml of simulated saliva pH 6.8. A tablet having amaranth powder on the upper surface was placed on the filter paper. Time required to develop red color on the upper surface of tablet was recorded as wetting time. Three tablets from each formulation were randomly selected and the average wetting time was noted. Wetting time corresponds to the time taken for the tablet to disintegrate when placed gently on the tissue paper in a petridish. This method will duplicate the *in-vivo* disintegration as the tablet is motionless on the tongue. Less wetting time indicates more porous the tablets.

The wetted tablet was then weighed. Water absorption ratio, R, was determined using equation –

$$R = 10 \times Wa - Wb/Wb$$

Where, Wb = weight of the tablet before water absorption

Wa = weight of the tablet after water absorption

Three tablets from each formulation were performed and standard deviation was also determined.

***In vitro* disintegration time**

Six healthy human volunteers were selected and their written consent was obtained. Each volunteer randomly took one tablet and kept on the tongue. The time taken for complete disintegration of the tablet on the tongue was noted. It is expressed in seconds. After the test, mouth was washed with distilled water. Three trials were performed with 2 days interval, between trials.

Test for dispersion

This test is carried out for dispersible tablets. Two tablets were placed in 100 mL of water and stirred gently until it was completely dispersed and smooth dispersion was obtained. The dispersed liquid was passed through sieve no. 22. No residue should remain over the sieve

Mouth feel

The same human volunteers participated in taste evaluation test, were asked to give their opinion about the feeling of smoothness or grittiness of the dispersion soon after the tablet got disintegrated.

***In vitro* Dissolution studies**

In vitro dissolution studies for all the fabricated tablets was carried out by using USP Type II apparatus (USP XXIII Dissolution Test Apparatus) at 50 rmp in 900 ml of phosphate buffer pH 6.8, maintained at 37±0.5ºC. 5 ml aliquot was withdrawn at the specified time intervals, filtered through whatmann filter paper and assayed spectrophotometrically at 265nm using double beem UV/Visible spectrometer. An equal volume of fresh medium, which was pre warmed at 37 ºC was replaced into the

dissolution medium after each sampling to maintain the constant volume throughout the test. Dissolution studies were performed in triplicate[11-16].

Stability Studies

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, light and enables recommended storage conditions, re-test periods and shelf lives to be established.

ICH specifies the length of study and storage conditions:

- Long term testing 25°C ± 2°C / 60 % RH ± 5 % for 12 months 207
- Accelerated testing 40°C ±2 °C / 75 % RH ± 5 % for 6 months.

In the present study, stability studies were carried out at 25°C ± 2°C / 60 % RH ± 5 % and 40°C ±2 °C / 75 % RH ± 5 % for a specific time period up to 30 days for the selected formulations. Tablets were evaluated for hardness, weight variation, friability, content uniformity, disintegration and drug release[17].

RESULTS AND DISCUSSION

Now a day's MD tablets are palying vital role in the market. Many patients, especially elderly find it difficult in swallowing tablets, capsules, fluids and thus do not comply with prescription, which results in high incidence of non-compliance oriented research has resulted in bringing out many safer and newer drug delivery systems. Rapidly disintegrating/dissolving tablet is one of such example, for the reason of rapid disintegration or even with saliva. Significance of this drug delivery system includes administration without water, accuracy of dosage, ease of portability, alternative to liquid dosage forms, ideal for paediatric and geriatric patients and rapid onset of action.

Mouth disintegrating tablets of Famotidine were prepared by adding natural superdisintegrating agent i.e. Treated agar and *Hibiscus rosasinensis Linn* mucilage.

IR spectra of Famotidine and its physical mixture with formulation excipients were determined using FT-IR. and found, there is no interaction between the drug and excipients.The pre-compression parameters of all the formulations were depicted in the Table 2. The angle of repose, bulk density, tapped density, carr's index and hausner's ratio shows good flowability in almost all the formulations resulting suitable for the preparation of MD tablets.

The prepared tablets were evaluated for different parameters and results were depicted below.

Thickness of the formulations FHR1 to FHR4 varied from 2.90±0.33 to 3.02±0.35 mm while of formulations FTG1 to FTG4 showed from 2.86±0.48 to 2.99±0.99 mm respectively. The hardness was uniformly maintained and it was found to be within 2.9±0.23 to 3.5±0.35 kg/cm^2. Percent friability was less than 1% in the entire formulations and the values obtained lies within 0.32±0.13 to 0.78±0.11 and found with in the range only. The percentage weight variation for all the formulation are tabulated in Table No.2. All the tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits of ±7.5%. The percentage drug content of all the tablets were found to be between 99.21±0.13 to 102.45±0.41, which was within the acceptable limits.

The internal structure of tablets that is pore size distribution, water penetration into tablets and swelling of disintegration substance are suggested to be the mechanism of disintegration. Tablets from each batch show immediate disintegration. Disintegration time decreases with increase in concentration of the disintegrants. Disintegration time was given in Table-2. The rapid disintegration was seen in the formulation FHR4 containing HR mucilage as disintegrating agent. This is due to the rapid uptake of water from the medium, swelling and burst effect. As in the treated agar also same. As the concentration increases the disintegration time decreases profoundly. This is due to formation of pores when agar is treated with water, where the pores formed, which decreases time.

The wetting time was rapid in all the formulations. Wetting is closely related to inner structure of tablets. This may be due to ability of swelling and also capacity of absorption of water. L-HPC is having high water absorption capacity and cause swelling. The results were depicted in the **table 2**. The water absorption ratio that is the uptaking of water was very fast and which that ratio found higher. Comparison

of wetting time is also done with *in vitro* disintegration time and wetting time which that shown in **Figure1**.

Dissolution profile of the formulations FHR1, FHR2, FHR3 and FHR4 and formulations FTG1, FTG 2, FTG 3, FTG 4 is shown in Figure-2. As the concentration of the polymer increased there was decrease in the disintegration time and increase in dissolution of drug. 90% of the drug was released from the all the formulations with in 10 minutes, which the results were depicted in the **Table 2**.

From drug release it was observed that increase in concentration of superdisintegrant increases the drug release. Therefore formulation FHR4 and FTG 3 was selected as the optimized formulation as it showed good release, good wetting property, and good precompression and good post compression results.

All the healthy human volunteers for taste masking evaluation, none of the formulation show any bitter taste when tablets are held in the mouth, which shows excellent taste masking effect of the aspartame and flavors and pleasant mouth feeling, thus considered the fulfillment requirements of mouth dissolving tablets.

The porous structure is sole responsible for water uptake, which facilitates wicking action of mucilage and treated agar in bringing about faster disintegration. From the values obtained, it is proved that all the formulations FHR1 to FHR4 and FTG1 to FTG4 dissolution (release) of the drugs follows first order.

The optimized formulations FHG4 and FTG3 were kept for accelerated stability and monitored for appearance, hardness, friability, drug content, *in vitro* dispersion time, *in vivo* disintegration time, wetting time and dissolution profile study and found to stable for all the different parameters.

Lastly, Thus, the mucilage of *Hibiscus Rosa-sinensis* Linn and modified treated agar can be used in the preparation of mouth dissolving tablets as superdisintegrants. These natural polymers are economic and are also easily available in the nature.

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Table 1: Compositions of Famotidine Mouth Dissolving Tablets

Sr. No	Ingredients	FHR1	FHR2	FHR3	FHR4	FTG1	FTG2	FTG3	FTG4
1	Famotidine	20	20	20	20	20	20	20	20
2	Mucilage of *Hibiscus Rosa-sinensis Linn*	6	12	18	24	_	_	_	_
3	Treated agar	_	_	_	_	8	16	24	32
4	L-HPC	25	25	25	25	25	25	25	25
5	Avicel pH 102	60	60	60	60	60	60	60	60
6	Lactose	71	65	59	53	69	61	53	45
7	Aspartame	8	8	8	8	8	8	8	8
8	Talc	4	4	4	4	4	4	4	4
9	Mg. Stearate	6	6	6	6	6	6	6	6

Table 2: Evaluation Parameters of Famotidine Mouth Dissolving Tablets

Formulation code / **Parameters**	FHR1	FHR2	FHR3	FHR4	FTG1	FTG2	FTG3	FTG4
Angle of repose(o)	32°96	31°47′	27° 47′	26º47′	28º60′	′27º10′	28º60′	25º53′
Carr's index (%)	16.75±0.59	15.25±0.79	16.36±0.19	17.63±0.35	17.33±0.55	16.29±0.61	15.66±0.95	15.34±0.38
Thickness (mm) ± SD	2.95±0.58	2.90±0.33	3.01±0.38	3.02±0.35	2.86±0.48	2.96±0.98	2.96±0.08	2.99±0.99
Hardness(kg/cm2)	3.5±0.35	2.9±0.23	3.2±0.56	3.3±0.87	3.2±0.12	3.4±0.91	3.3±0.36	3.3±0.32
Drug content (%) ± SD	99.21±0.13	99.36±0.65	101.03±0.27	99.86±0.65	99.87±0.06	102.45±0.41	101.0±0.69	100.2±13
Weight variation (mg) ± SD	199±0.65	201±0.52	201±0.23	201±0.13	200±0.03	202±0. 29	201±0.11	200±0.53
Friability (%) ±SD	0.56±0.12	0.65±0.85	0.32±0.13	0.37±0.25	0.78±0.11	0.42±0.25	0.38±0.29	0.57±0.13
***In vitro* disintegration time (sec)**	46s	36s	28s	22s	30s	22s	15s	12s
***In vitro* Dispersion time(sec)**	54s	45s	37s	31s	38s	25s	18s	16s
Water absorption ratio(Sec)	88.3 ± 0.36	87.2±0.23	88.03±0.56	81.05±0.14	85.32±0.65	84.24±0.41	86.36±0.54	88.52±0.52
Wetting time (Sec)	69s	62s	52s	48s	51s	45s	36s	28s
Cum. % Drug Released	96.32	97.65	98.63	99.37	96.52	99.53	99.95	98.98

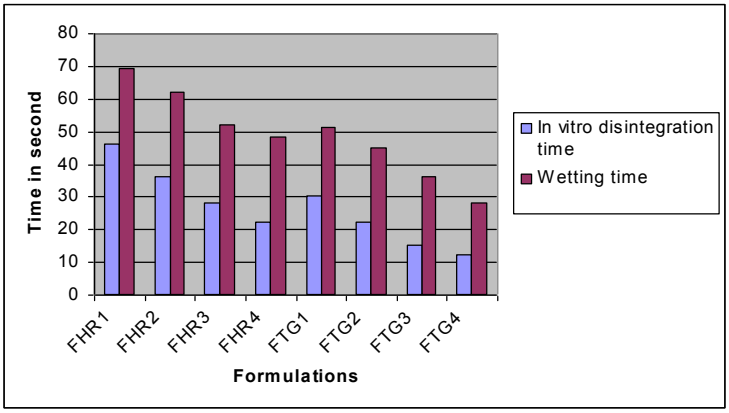

Fig 1: Comparison of Disintegration Time with Wetting Time Of All The Formulations

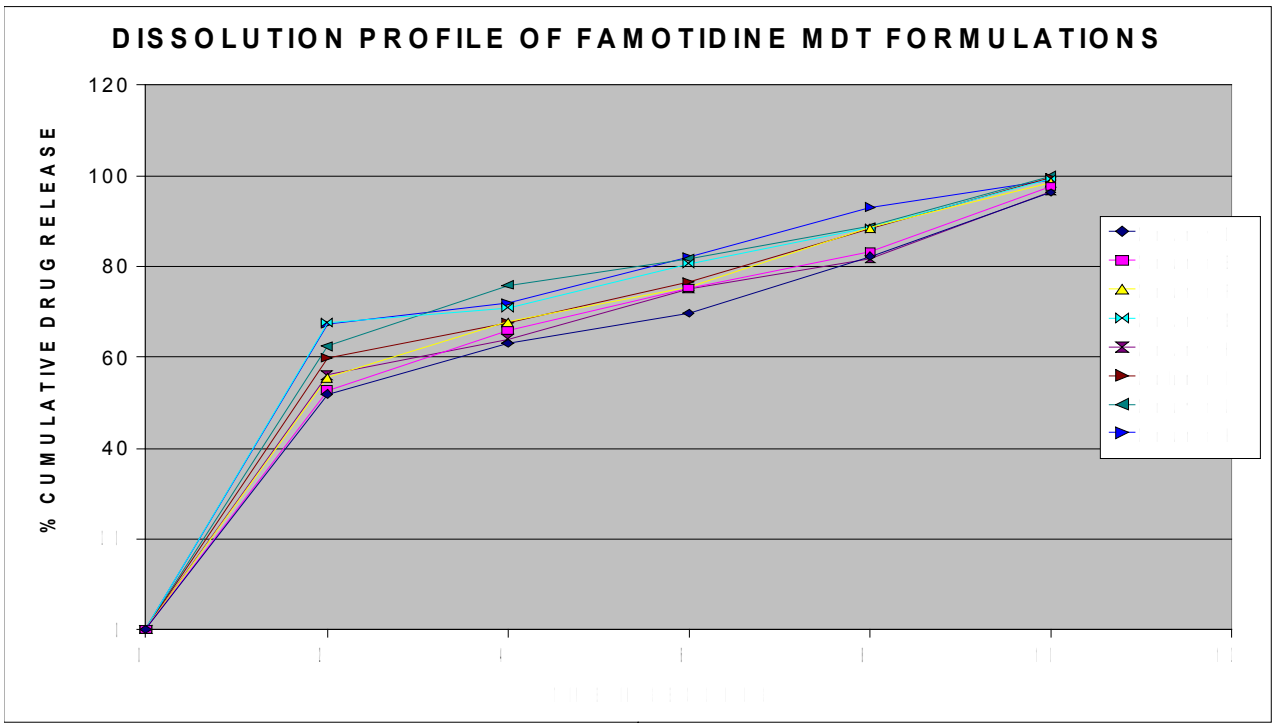

Fig 2: Dissolution Profile Of Famotidine Mouth Disintegrating Tablet Of All Formulations

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