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Research Article

FORMULATION, DEVELOPMENT AND EVALUATION OF GASTRORETENTIVE MUCOADHESIVE TABLETS OF FAMOTIDINE USING NATURAL POLYMERS

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Abstract

Mucoadhesive drug delivery systems prolong the residence time of the dosage form at the site of application or absorption. They facilitate an intimate contact of the dosage form with the underlying absorption surface and thus improve the therapeutic performance of the drug. The formulation development of Famotidine mucoadhesive tablets involved a comprehensive assessment of post-compression properties, as well as the determination of mucoadhesive strength. The in vitro drug release study of Famotidine mucoadhesive tablets, particularly for formulation F5, was conducted over a specified time period ranging from 0.5 to 12 hours. The release profile displayed a gradual and sustained release of Famotidine over the designated time intervals, with the cumulative percentage release increasing from 22.65% at 0.5 hours to 99.45% at 12 hours.

Introduction

Oral route of drug administration is the most convenient and commonly used method of drug delivery. However, this route has several physiological problems. Including an unpredictable gastric emptying rate that varies from person to person, a brief gastrointestinal transit time (80-12h), and the existence of an absorption window in the upper small intestine for several drugs These difficulties have prompted researchers to design a drug delivery system which can stay in the stomach for prolonged and predictable period. Attempts are being made to develop a drug delivery system which can provide therapeutically effective plasma drug concentration for a longer period, thereby reducing the dosing frequency and minimizing fluctuation in plasma drug concentration at steady state by delivering the drug in a controlled and reproducible manner .
sdrug delivery system). Dosage forms that can be retained in the stomach are called GRDDs. GRDDSs can improve the controlled delivery of drugs that have an absorption window by continuously releasing the drug for a prolonged period of time before it reaches its absorption site .
Prolonging the gastric retention of the drugs is sometimes desirable for achieving therapeutic benefits of drug that are absorbed from the proximal part of the GIT (gastro intestinal tract) or those are less soluble in or are degraded by alkaline pH or they encounter at the lower part of the GIT. GRDDS are beneficial for such drugs by improving their .

- Bioavailability
- Therapeutics efficiency and
- Possible reduction of the dose
- Apart from these advantages, these systems offer various pharmacokinetic advantages like, maintenance of constant therapeutic levels over a prolonged period and thus reduction in fluctuation in the therapeutic levels.

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Drugs that are easily absorbed from GIT and have short half-lives are eliminated quickly from the systemic circulation. Frequently dosing of these drugs is required to achieve suitable therapeutic activity.
To avoid this limitation, the development of oral sustained controlled release formulations is an attempt to release the drug slowly into the GIT and maintain an effective drug concentration in the systemic circulation for a long time.
After oral administration, such a drug delivery would be retained in the stomach and release the drug in controlled manner, so that the drug could be supplied continuously to its absorption sites in the GIT [5.]
GRDD Devices are primarily site specific drug delivery systems, which gets retained in the stomach for longer period of time, thus helping in absorption of drug for the intended duration of time. This in turn improves:

- Bioavailability
- Reduce drug wastage
- Improves solubility of drugs that are less soluble at high pH environment (e.g. weakly basic drug like domperidone, papaverine)
- Also helps in achieving local delivery of drug to the stomach and proximal small intestine.

To formulate a site specific orally administered controlled release dosage form, it is desirable to achieve a prolong gastro residence time by the drug delivery.[1-4]

Materials and Methods

Method For Preparation Of Famotidine Gastroretentive Mucoadhesive Tablet [5-13]

Famotidine, polymers, and excipients were mixed thoroughly and passed though sieve 60. The tablets with different composition (Table 7.1) were prepared by direct compression technique on a rotary punch tablet compression machine (Rimek mini press, MT-Il, India). The powder was weighed and individually filled in the die cavity (8 mm diameter), and constant pressure was applied. The tablets were evaluated for various parameters like thickness, average weight, hardness, drug content, swelling index, mucoadhesive strength and in vitro drug release 1841.
Polymers selected for tablets are:

- HPMC K4
- Sodium alginate
- Gum tragacanth

7.1.1 Optimization of mucoadhesive tablets of Famotidine

Table 7.1: Various formulations of Famotidine mucoadhesive tablets

Excipients (mg)						
Famotidine	40	40	40	40	40	40

HPMC K4	25	50	25	50	25	50
Sodium alginate	20	30			30	40
Gum tragacanth			20	30	30	40
MCC	95	60	95	60	55	10
Talc	10	10	10	10	10	10
Mg Stearate	10	10	10	10	10	10
Total Weight	200	200	200	200	200	200

Excipients like Sodium alginate, Gum tragacanth, as mucoadhesive polymers. Steps associated with the manufacture of tablets, required amount of API, polymer and excipients were weighed legitimately and transferred into polyethylene pack and the mix was blended for not less than 15 min. The mix acquired was then lubricated by including Talc and magnesium stearate and again blended for another 5min.

7.2 Evaluation Of Powder Blend

There are many formulations and process variables involved in mixing step and all these can affect characteristics of blend produced, bulk density, true density and percent compressibility index have been measured which are given in table 8.1.

7.2.1 Bulk density

Bulk density is determined by measuring the volume of a known mass of powder sample that has been passed through a screen into a graduated cylinder or through a volumetric measuring apparatus into a cup.

Procedure:- A known quantity of powder was poured into the measuring cylinder carefully level the powder without compacting, if necessary and read the unsettled apparent volume, Vo, to the nearest graduated unit. Calculate the bulk density, in gm per ml gm/ml, by the formula

Bulk density = Bulk Mass/ Bulk Volume

7.2.2 Compressibility index (Carr's index):

Compressibility index (C.I.) is an important measure that can be obtained from the bulk and tapped densities. Carr's index a material having values of less than 20% to 30% is defined as the free flowing material. It can be calculated as per given formula:

$$C.I. = \frac{\text{Tapped density - Bulk density}}{\text{Tapped density}} \times 100$$

7.2.3 Hausner ratio:

It indicates the flow properties of the powder and it can be measured by the ratio of tapped density to bulk density.

Hausner ratio = Tapped density / Bulk Density

7.3 Evaluation of tablets

All the tablets were evaluated for following various parameters which includes;

7.3.1 General Appearance

Five tablets from various batches were randomly selected and organoleptic properties such as color, odor, taste, shape, were evaluated. Appearance was judged visually. Very good (+++), good (+4), fair (+) poor (-), very poor (- -) [85].

7.3.2 Thickness and diameter

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

7.3.3 Drug content

Twenty tablets were taken and amount of drug present in each tablet was determined. The tablets were crushed in a mortar and the powder equivalent to 10mg of drug was transferred to 10ml standard flask. The powder was dissolved in 5 ml of 0.1 N HCI and made up to volume with of 0.1 N HCI. The sample was mixed thoroughly and filtered through a 0.45g membrane filter. The filtered solution was diluted suitably and for drug content by UV spectrophotometer at max of 265.0 nm using O. I N HCI blank [861].

7.3.4 Hardness

For each formulation the hardness of five tablets was resolved utilizing the Monsanto hardness tester (Cadmach).

7.3.5 Friability

The friability of sample of 10 tablets was estimated utilizing 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 [87].

7.3.6 Uniformity of weight

Twenty tablets were randomly selected from each batch individually weighed, the average weight and standard deviation of 20 tablets was calculated.

7.3.7 Swelling Index

Swelling study of individual polymers and combinations was carried out using eight-stage USP type I (basket) Dissolution Test Apparatus (Lab India, DS 8000) at 5() rpm, and 0.1 N HCI was used as medium, and the temperature was maintained at 37 ± 0.5 ^{0}C. Weight of individual tablet was taken prior to the swelling study (WI). The tablet was kept in a basket. The weight of tablet was taken at time interval of 2, 4, 8, 12 hours (W2). Percent hydration

(swelling index) was calculated as shown in Table 7.4 using the following formula:

Swelling index = (W2 - WI) x 100/W2

Where WI is the initial weight of tablet and W2 is the weight of hydrated tablet.

7.3.8 Determination of mucoadhesive strength

The working of a double beam physical balance formed the basis of the bioadhesion test assembly. The left pan was removed and hung with a stainless steel chain. A Teflon block with 1.5 in height and 1.5 in diameter was hung with the stainless steel chain to balance the weight of the other pan. The height of the total set up was adjusted to accommodate a glass container or beaker below it leaving a head space of about 0.5 cm in between. Block of 2 in height and 1.5 in diameter was kept inside the glass vessel, which was then positioned below the top hung Teflon block. Suitable weights were added on the right pan to balance the beam of the balance. The porcine gastric mucosa was attached with the mucosal side upward onto the lower Teflon block which was then placed in the glass

vessel. Sufficient simulated gastric fluid was filled into the beaker so that the surface of the fluid just touches the mucosal surface to Teflon block [881. A tablet was fixed to the bottom portion of the cylindrical shaped base with 'feviquick' glue. The string with tablet was hung in such a way that the tablet was just in contact with the surface of the mucosal side of pig stomach when the balance was in a balanced position. The balance was left in a balanced position for fixed time of 5 minutes and then slowly weights were increased on the right pan until the tablet detaches from the surface of the intestinal mucosa. The weights on right side pan gave the mucoadhesive strength of the tablet in grams. From mucoadhesive strength, the bioadhesion force was calculated per unit area of the tablet as follows.

$$F = \frac{Ww \times G}{a. \times A}$$

Where F is the bioadhesion force (kg/m/s^2), ww is the mass applied (g), g is the acceleration due to gravity (cm/s^2) and A is the surface area of the patch (cm^2).

7.3.9 Dissolution rate studies

In vitro drug release of the sample was done using USP-type Il dissolution apparatus (Paddle type). The dissolution medium, 900 ml 0.1 N HCI was set into the dissolution flask maintaining the temperature of 37±0.5 ^{0}C and rpm of 75. One Famotidinetablet was set in every container of dissolution apparatus. The mechanical assembly was permitted to keep running for 10 hours. Sample measuring 5 ml were pulled back after each I hour up to 2 hours using pipette. The new disintegration medium (37^{0}C) was supplanted each time with a similar amount of the sample and takes the absorbance at 264.0 nm using spectroscopy.

Results and Discussions

Post Compression Properties Of Famotidine Mucoadhesive Tablets

The post-compression properties of Famotidine mucoadhesive tablets, as characterized by thickness, hardness, weight variation, friability, and drug content, provide crucial insights into the final product's physical attributes, mechanical strength, uniformity, and drug dosage consistency.

Thickness: The tablet thickness for formulations FI to F6 ranges from 2.1 mm to 2.4 mm. These values indicate reasonable uniformity in tablet dimensions, ensuring consistency in dosing and ease of handling.

Hardness: Tablet hardness, a measure of the tablet's mechanical strength, is reflected in values ranging from 5.3 kg/cm^2 to 5.6 kg/cm^2. These values suggest that the tablets possess adequate hardness, crucial for structural integrity, handling during packaging, and resistance to mechanical stresses during transit and use.

Weight Variation: The weight variation values, ranging from 198 mg to 205 mg, indicate consistency in the tablet weight among different units within each formulation. This is vital for ensuring uniform drug content and therapeutic efficacy across tablets in a batch.

Friability: Friability, calculated as the percentage of weight loss during tablet abrasion, is observed to be low, ranging from 0.744% to 0.856%. These low values suggest minimal tablet abrasion and indicate that the tablets can withstand the mechanical stresses encountered during packaging, transportation, and handling.

Drug Content: The drug content values range from 97.54% to 99.85%, indicating the amount of Famotidine present in each tablet relative to the intended dosage. The high drug content values reflect the accuracy and precision of the formulation process, ensuring that each tablet delivers the desired therapeutic dose.

The post-compression properties collectively suggest that formulations Fl to F6 of Famotidine mucoadhesive tablets exhibit favorable physical charactenstics, mechanical strength, weight uniformity, and drug content consistency. The tablets meet the standard requirements for thickness, hardness, weight variation, friability, and drug content, indicating their potential for reliable clinical performance. The low friability values affirm the tablets' robustness during handling and transportation. These results collectively demonstrate the successful formulation and manufacturing of Famotidine mucoadhesive tablets with the desired attributes for effective drug delivery and patient compliance.

Table 8.2: Results Of Post Compression Properties OfFamotidine Mucoadhesive Tablets

Figure 8.2: Results of post compression properties of mucoadhesive tablets

Swelling index

The swelling index results of Famotidine mucoadhesive tablets reveal significant insights into the tablets' mucoadhesive behavior over time. The formulations, denoted as Fl to F6, exhibit a time-dependent increase in the swelling index, indicating their ability to absorb water and undergo controlled swelling. Notably, all formulations demonstrate a consistent rise in the swelling index from 2 hrs to 12 hrs, with the maximum values reached at the latter time point.

This sustained swelling is essential for mucoadhesive formulations, suggesting prolonged contact with the mucosal surface, which is crucial for achieving prolonged drug release and enhancing therapeutic efficacy. Variability among formulations in terms of swelling characteristics implies differences in composition and formulation parameters, which can influence the tablets' hydration and swelling properties. The observed higher swelling indices may have implications for sustained drug release, making these formulations promising candidates for applications requiring prolonged therapeutic action.

Table 8.3: Results of Swelling Index of Famotidine mucoadhesive tablets

Formulation code	% Swelling Index			
	2 hrs.	4 hrs.	8hrs.	12hrs.
F1	45.56	65.58	85.56	99.23
F2	52.32	72.32	92.32	105.65
F3	55.65	69.98	83.35	92.65
F4	64.56	75.65	95.56	105.98
F5	78.89	98.89	102.32	120.32
F6	65.58	83.32	98.87	100.65

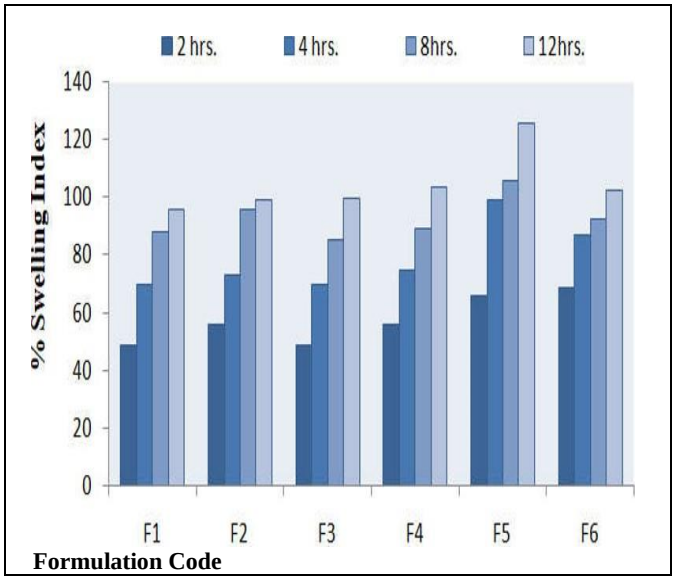

Figure 8.3: Results of Swelling Index of Famotidine mucoadhesive tablets

Mucoadhesive strength

In vitro mucoadhesive strength was carried out by using self-fabricated instrument. Results for in vitro force of adhesion were shown in Table no.8.4.

Table 8.4: Results of determination of mucoadhesive strength

S. No.	Formulation Code	Force of Adhesion
1	**F1**	2.45
2	**F2**	3.65
3	**F3**	3.25
4	**F4**	3.36
5	**F5**	2.85
6	**F6**	3.12

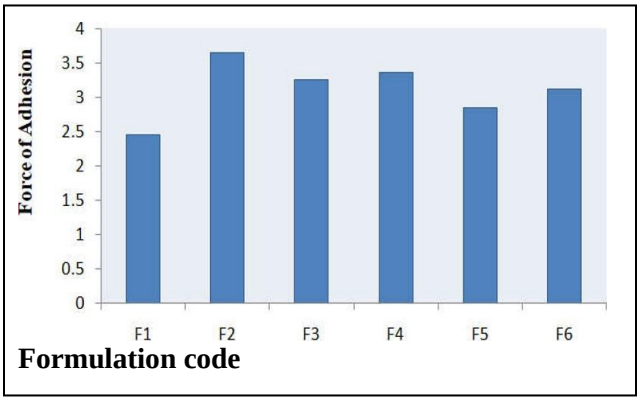

Figure 8.4: Graph of determination of mucoadhesive strength

In vitro drug release study ofmucoadhesive tablet

In vitro drug release studies were performed by using USP XXIII dissolution test apparatus Il at 50rpm using 900 mL of 1.2 pH buffer maintained at 37±0.5 ^{0}C as the dissolution medium.

The in vitro drug release profiles for the preliminary formulations were tabulated in Table no 8.5. The plot of cumulative percentage drug release v/s time (Hrs) for preliminary formulations were plotted and depicted in Figure.

Table 8.5: In-vitro drug release study of mucoadhesive tablets

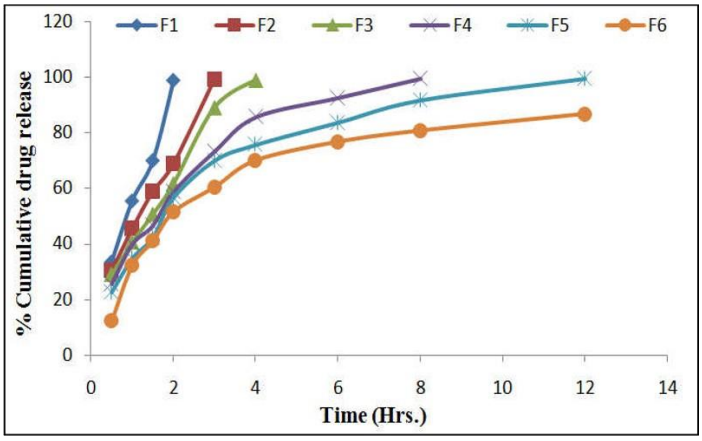

Figure 8.5: In-vitro drug release study of mucoadhesive tablets

Release kinetics of Famotidine mucoadhesive tablets

Table 8.6: In-vitro drug release data for optimized formulation F5.

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Formulation code	Thickness * (mm)	Hardness (kg/cm^2) n=3	Weight variation (mg) n=3	Friability (%) n=3	Drug content (%) n=3
F1	2.3	5.3	202	0.752	98.65
F2	2.2	5.4	198	0.856	98.85
F3	2.4	5.5	205	0.745	98.12
F4	2.2	5.6	203	0.752	97.85
F5	2.1	5.5	201	0.854	99.85
F6	2.3	5.3	199	O. 744	97.54

Table 8.2: Results Of Post Compression Properties Of Famotidine Mucoadhesive Tablets

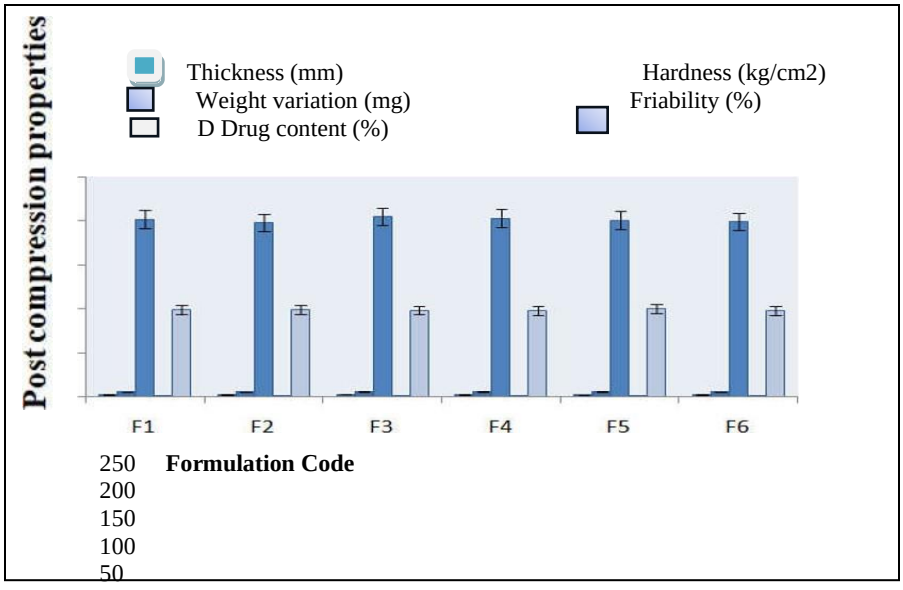

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Figure 8.2: Results of post compression properties of mucoadhesive tablets

Table 8.5: In-vitro drug release study of mucoadhesive tablets

Time	% Cumulative Drug Release					
(hr)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
0.5	33.45	30.45	28.98	25.65	22.65	12.25
1	55.48	45.58	40.65	39.98	34.85	32.25
1.5	69.98	58.89	50.65	46.65	42.32	40.95
2	98.85	68.78	61.56	58.78	56.65	51.47
3	-	99.12	88.98	73.36	69.98	60.36
4	-	-	98.85	85.65	75.65	69.98
6	-	-	-	92.56	83.65	76.65
8	-	-	-	99.45	91.65	80.65
12	-	-	-	-	99.45	86.65

Release kinetics of Famotidine mucoadhesive tablets

Table 8.6: In-vitro drug release data for optimized formulation F5

Time (h)	Square Root of $\mathbf{Time(h)^{1/2}}$	Log Time	Cumulative* % Drug Release	Log Cumulative % Drug Release	Log Cumulative % Drug Remaining	Log Cumulative % Drug Remaining
0.5	0.707	-0.301	35.56	1.551	64.44	1.809
1	1	0	40.23	1.605	59.77	1.776
1.5	1.414	0.301	45.65	I .659	54.35	1.735
2	2	0.602	52.32	1.719	47.68	1.678
3	2.449	0.778	65.85	1.819	34.15	1.533
4	2.828	0.903	73.32	1.865	26.68	1.426
6	3.464	1.079	79.98	1.903	20.02	1.301
8	0.707	-0.301	84.65	1.928	15.35	1.186
12	1	0	98.78	995	1.22	0.086