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FORMULATION AND EVALUATION OF FAMOTIDINE SUSTAINED RELEASE TABLETS CONTAINING CHAMOMILE MUCILAGE

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ABSTRACT

GERD is common in Western countries, with prevalence ranging from 13% to 20% in the United States and 9.8% to 18% in Europe, while it is lower in Asia (2.5-4.8%). Traditional pharmacological therapy necessitates the administration of therapeutic substances on a regular basis. Sustained Release suitable for overcoming pharmacological side effects and increasing therapeutic efficacy. Thus merging the advantages of sustained release tablet & natural polymer, this study deals with formulation and evaluation of famotidine sustained release tablets containing chamomile mucilage. The formulation & evaluation of tablet was performed according to standard protocol. Results showed that, in total nine formulations the bulk density varied from 0.315 to 0.341 gm/ml while the tapped density ranged from 0.432 to 0.465 gm/ml. The compressibility index spans from 24.330 to 27.742. Further the Hausner ratio extends from 1.325 to 1.384. From the results of post compression parameter it was seen that the maximum drug content was found to be 99.45 % in F7 formulation. The total floating time was greater than 12 hrs for all formulations. The thickness varied from 3.09 to 3.26 mm while the hardness ranged from 6.3 to 6.9 kg/cm2. The weight variation was seen in between 296 to 305 mg while the friability ranged from 0.745 to 0.895%. Further the floating lag time was found to be lowest for F7 which is 25±2 sec while highest for F1 which is 55±3 seconds. The In-vitro drug release study of FGR tablets proved that about 99.74 % drug is released in 12 hrs. The formulated tablet follows peppas model of drug release kinetics which is evident from R^2 value of 0.952. Thus, formulation F7 have all the ideal parameters & hence can be used for treating GERD.

Keywords: Gastroesophageal reflux disease. Famotidine, sustained release tablets, chamomile, mucilage, Natural polysaccharide.

INTRODUCTION

Gastroesophageal reflux disease (GERD) is defined as "a condition that occurs when stomach contents reflux causes bothersome symptoms and/or complications." Heartburn and regurgitation are common esophageal symptoms, as are chest pain and dysphagia. Chronic cough, hoarseness, asthma, and dental erosions are examples of extra-esophageal symptoms or indications that have been linked to GERD in population-based research. However, these symptoms have alternative aetiologies other than GERD, and the causative involvement of reflux remains difficult to substantiate in the absence of associated classic

GERD symptoms. Mucosal damage is the most prevalent GERD complication, with reflux esophagitis, strictures, Barrett's oesophagus, and adenocarcinoma being the most common [1-2].

GERD is common in Western countries, with prevalence ranging from 13% to 20% in the United States and 9.8% to 18% in Europe, while it is lower in Asia (2.5-4.8%). Obesity, advancing age, a family history of reflux illness, and long-term use of certain medicines (nitrates, calcium antagonists, benzodiazepines, and so on) are all risk factors. GERD is a chronic condition with recurrence and remission stages over time, although it is a benign disorder in terms of prognosis [3-4].

Traditional pharmacological therapy necessitates the administration of therapeutic substances on a regular basis. These agents are designed to have the highest possible stability, activity, and bioavailability. Traditional drug administration methods are successful for the majority of medications, however some are unstable or poisonous, and have narrow therapeutic ranges. Some medications can have solubility issues. In such instances, a method of continuous therapeutic agent administration is preferable to maintain constant plasma levels. Controlled drug delivery systems were established three decades ago to address these issues. These delivery systems have several advantages over traditional systems, including increased efficiency, decreased toxicity, and increased patient convenience. The primary purpose of controlled drug delivery systems is to increase the efficacy of pharmacological therapy [5,6].

Sustained Release is also suitable for overcoming pharmacological side effects and increasing therapeutic efficacy. The fundamental concepts of sustained drug delivery systems optimise different factors such as biopharmaceutical, pharmacokinetic, and pharmacodynamic properties of a drug in such a way that therapeutic efficacy is maximised, side effects are minimised, and disease cure is easily attained. Sustained release drug delivery has several advantages in the pharmaceutical field, including improved patient compliance, reduced dose frequency, reduced fluctuation in steady-state drug levels, maximum utilisation of the drug, increased safety margin of potent drug, reduced healthcare costs through improved therapy, and shorter treatment period [7,8].

The synthetic polymers have low biocompatibility, the production of acidic chemicals during breakdown that can trigger systemic and local responses, and rapid mechanical strength loss are all characteristics of synthetic polymers utilised in tissue engineering. Natural polymers are increasingly being used. The use of natural plant-derived polysaccharides as excipients in the pharmaceutical industry has expanded because they can address formulation issues and lessen the negative effects of synthetic polymers [9,10].

Mucilages are natural metabolic products that are generated in the cell and do not dissolve easily in water. Mucilages can be found throughout the plant. Mucilage is a thick, sticky substance that practically all plants and some microbes create. Gums and mucilages have certain similarities in that they are both plant

hydrocolloids. They are also composed of transparent amorphous polymers and monosaccharide polymers, as well as uronic acid [11].

Chamomile (Matricaria chamomilla L.) is a well-known Asteraceae family medicinal plant that is sometimes referred to as the "star among medicinal species." It is now a popular and widely used therapeutic herb in folk and traditional medicine. Chamomile is primarily used as an anti-inflammatory and antibacterial, as well as an antispasmodic and mild sudorific. It is primarily used internally as a tisane (infuse 1 tablespoon of the drug in 1 L of cold water without heating) for stomach pain, sluggish digestion, diarrhoea, and nausea; and, more rarely and very effectively, for inflammation of the urinary tract and painful menstruation. Externally, the medicine in powder form can be administered to slow-healing wounds, skin eruptions, and infections like shingles and boils, as well as haemorrhoids and irritation of the mouth, throat, and eyes [12-13]. Thus merging the advantages of sustained release tablet & natural polymer, this study deals with formulation and evaluation of famotidine sustained release tablets containing chamomile mucilage.

MATERIALS AND METHODS

Procurement of drug

Famotidine was obtained as gift sample from Torrent Pharmaceutical Ltd., India.

Chemicals & Reagents

Xanthan gum, Chamomile mucilage, Carbopol 940 P, Chitosan, Citric acid, NaHCO3. Mg $(C_{18}H_{35}O_2)_2$, Talc, Lactose, etc. were obtained from S. D fine chemicals Mumbai. All chemicals & reagents obtained were of analytical grade.

Preparation of Chamomile Mucilage: a. Begin by collecting dried chamomile flowers. Ensure that they are clean and free from contaminants. b. Grind the dried chamomile flowers using a blender or mortar and pestle to break down the plant material and release the mucilage. c. Add a suitable amount of distilled water to the ground chamomile flowers to form a thick paste. The water-to-flower ratio can vary but typically ranges from 1:2 to 1:5 (w/v). Stir well to ensure even mixing.

Extraction of Mucilage: a. Heat the mixture gently over a water bath or on a hot plate. Maintain the temperature below boiling point. b. Continue stirring the mixture to facilitate the extraction of mucilage into the water. The heating and stirring can be carried out for a specific period, such as 30-60 minute [14].

Filtration: a. After extraction, allow the mixture to cool down to room temperature. b. Filter the mixture through a cheesecloth or fine mesh strainer to separate the liquid mucilage extract from the residual plant material.

Drying of Isolated Mucilage: a. Dry the isolated mucilage by spreading it in a thin layer on a glass surface or a suitable container. b. Place the mucilage in an oven or drying chamber at a low temperature (around 40-50°C) until it is completely dried. This can take several hours to a day, depending on the drying conditions.

Collection and Storage: a. Once fully dried, collect the chamomile mucilage, which will be in the form of a dry powder.

b. Store the isolated mucilage in a clean, airtight container away from moisture and light.

Method for preparation of Famotidine sustained release tablets

Direct compression was taken after to manufacture the gas generating floating tablets of Famotidine. Nine different formulations (F1, F2, F3, F4, F5, F6, F7, F8, and F9) were set up by direct compression. Every one of the polymers chose, drug and excipients were gone through strainer no. 40 preceding utilizing into plan. The sum and proportion of drug and polymers were weighed according to given in table no.1 and all the definition were utilized for encourage assessments parameters.

Optimization of sustained release tablets of Famotidine

Optimization of formulation carried out on the basis of OVAT (One variable at time) using amount of excipient used like Excipients like Xanthan gum, Gellan gum, Chitosan and Carbopol 940 P.

Table 1: Various formulations of sustained release tablets of Famotidine

Excipients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Famotidine	40	40	40	40	40	40	40	40	40
Xanthan gum	100	120	140	-	-	-	50	60	70
Chamomile mucilage	-	-	-	100	120	140	50	60	70
Carbopol 940 P	-	-	-	-	-	-	20	20	20
Chitosan	30	30	30	30	30	30	30	30	30
Citric acid	5	5	5	5	5	5	5	5	5
$NaHCO_3$	20	20	20	20	20	20	20	20	20
$Mg(C_{18}H_{35}O_2)_2$	10	10	10	10	10	10	10	10	10
Talc	5	5	5	5	5	5	5	5	5
Lactose	90	70	50	90	70	50	70	50	30
Total Weight	300	300	300	300	300	300	300	300	300

Evaluation of precompression parameter

Bulk density: Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. Accurately weighed amount of granules taken in a 50 ml capacity measuring cylinder was tapped for 100 times on a plane hard wooden surface and estimated the LBD and TBD. The LBD was calculated by dividing mass of powder by volume of packing. The TBD was calculated by dividing mass of powder by tapped volume of packing.

Carr's Compressibility index: Percent compressibility of powder mix was determined by Carr's compressibility index, calculated by using following formula:-

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

Hausners ratio: It is determined by dividing tapped density to the bulk density. Hausner's ratio value <1.25 shows better flow properties

Evaluation of tablets

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

General Appearance

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

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 [15].

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 HCl and made up to volume with of 0.1 N HCl. The sample was mixed thoroughly and filtered through a 0.45µ membrane filter. The filtered solution was diluted suitably and for drug content by UV spectrophotometer at λ_{max} of 264 nm using of 0.1 N HCl as blank.

Hardness

For each formulation, the hardness of five tablets was resolved utilizing the Monsanto hardness tester.

Friability

The friability of a 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.

Uniformity of weight

Twenty tablets were randomly selected from each batch individually weighed, the average weight and standard deviation of 20 tablets was calculated [16].

***In vitro* buoyancy studies:**

In vitro buoyancy was determined by floating lag time as per the method described by Rosa *et al.* The tablets were separately in a 100 ml glass beaker containing simulated gastric fluid, pH 1.2 as per USP. The time necessary for the tablet to increase to the outside and float was determined as floating lag time [86].

Dissolution rate studies

In vitro drug release of the sample was done using USP-type II dissolution apparatus (Paddle type). The dissolution medium, 900 ml 0.1N HCl was set into the dissolution flask maintaining the temperature of 37±0.5°C and rpm of 75. One prepared Famotidine tablet 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 1 hour up to 10 hours using 10ml pipette. The new disintegration medium

(37°C) was supplanted each time with a similar amount of the sample and takes the absorbance at 264nm using UV/Visible spectroscopy.

RESULTS & DISCUSSION

In this experiment total nine formulations were made and evaluated for various different characteristics. The bulk density varied from 0.315 to 0.341 gm/ml while the tapped density ranged from 0.432 to 0.465 gm/ml. The compressibility index spans from 24.330 to 27.742. Further the Hausner ratio extends from 1.325 to 1.384. All of the generated attributes of powder combinations had values within the limits, suggesting that the powder blends had the requisite flow property for tablet compression.

From the results of post compression parameter it was seen that the maximum drug content was found to be 99.45 % in F7 formulation. The total floating time was greater than 12 hrs for all formulations. The thickness varied from 3.09 to 3.26 mm while the hardness ranged from 6.3 to 6.9 kg/cm2. The weight variation was seen in between 296 to 305 mg while the friability ranged from 0.745 to 0.895%. Further the floating lag time was found to be lowest for F7 which is 25±2 sec while highest for F1 which is 55±3 seconds.

The In-vitro drug release study of FGR tablets proved that about 99.74 % drug is released in 12 hrs. The medication release was observed to be more delayed as the concentration of gum in the formulation increased. By raising the polymer concentration, a viscous gel layer is created that is resistant to erosion, and the drug diffusion is essentially controlled by the gel viscosity. The natural gum is hydrophilic, and it is utilised as an excipient to delay drug release in a controlled manner for up to 12 hours. The production of the matrix layer by the mucilage around the tablet caused the enlargement of the tablet, allowing it to maintain drug release. The swelled matrix retains more water as it swells, until shear forces in the dissolving liquid untangle the individual polymer chains from the matrix.

The regression analysis data of Famotidine sustain release tablets provided different values for different kinetics model. In case of zero order & first order reaction the R^2 value was noted to be 0.812 & 0.903. While for the Higuchi & Peppas the R^2 value was estimated to be 0.801 to 0.952.

Table 2: Result of pre-compression properties of Famotidine

Formulation Code	Bulk density(gm/ml)	Tapped density(gm/ml)	Compressibility index	Hausner ratio
F1	0.326	0.432	24.537	1.325
F2	0.341	0.453	24.724	1.328
F3	0.339	0.448	24.330	1.322
F4	0.321	0.436	26.376	1.358
F5	0.336	0.465	27.742	1.384
F6	0.315	0.432	27.083	1.371
F7	0.337	0.458	26.419	1.359
F8	0.329	0.436	24.541	1.325
F9	0.321	0.432	25.694	1.346

Table 3: Results of post compression properties of Famotidine sustain release tablets

Formulation code	Thickness (mm)	Hardness (kg/cm2) n=3	Weight variation (mg) n=3	Friability (%) n=3	Drug content (%) n=3	Total floating duration (h)
F1	3.12±0.25	6.3±0.05	302±0.86	0.658±0.17	98.78±0.36	>12
F2	3.09±0.48	6.4±0.03	305±0.53	0.662±0.28	98.12±0.38	>12
F3	3.15±0.82	6.8±0.05	300±0.96	0.745±0.18	98.65±0.29	>12
F4	3.15±0.38	6.9±0.08	298±0.82	0.895±0.46	98.65±0.46	>12
F5	3.26±0.53	6.8±0.03	301±0.72	0.658±0.17	97.74±0.18	>12
F6	3.14±0.41	6.7±0.06	296±0.81	0.774±0.18	98.12±0.25	>12
F7	3.15±0.69	6.8±0.09	293±0.63	0.798±0.23	99.45±0.28	>12
F8	3.14±0.57	6.7±0.09	298±0.48	0.762±0.26	98.78±0.33	>12
F9	3.16±0.88	6.9±0.05	297±0.73	0.736±0.11	98.45±0.28	>12

Table 4: Results of *in-vitro* buoyancy study of Famotidine sustain release Floating time

S. No.	Formulation Code	Floating lag times (sec)
1.	F1	55±3
2.	F2	48±5
3.	F3	35±6
4.	F4	45±2
5.	F5	42±4
6.	F6	38±7
7.	F7	25±2
8.	F8	36±3
9.	F9	40±5

Table 5: *In-vitro* drug release study of FGR tablets

Time	% Cumulative Drug Release								
(hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0.5	40.23	34.65	32.12	34.65	32.25	31.25	21.32	18.85	15.58
1	55.65	49.98	43.32	48.85	46.65	45.58	36.75	35.45	32.25
1.5	69.98	65.58	60.47	65.58	59.98	53.32	44.32	42.23	40.47
2	88.85	78.85	73.32	83.32	82.23	69.98	56.65	53.32	49.98
3	96.65	84.45	80.47	96.65	95.65	78.85	65.56	62.23	58.85
4	-	99.12	89.98	98.85	98.85	89.98	78.89	70.23	68.87
6	-	-	98.85	-	99.47	98.78	83.23	80.47	78.84
8	-	-	-	-	-	99.12	89.98	85.56	83.32
12	-	-	-	-	-	-	99.74	89.98	85.458

Table 6: *In-vitro* drug release data for optimized formulation F7

Time (h)	Square Root of Time(h)$^{1/2}$	Log Time	Cumulative*% Drug Release	Log Cumulative % Drug Release	Cumulative % Drug Remaining	Log Cumulative % Drug Remaining
0.5	0.707	-0.301	22.32	1.349	77.68	1.890
1	1	0	36.75	1.565	63.25	1.801
1.5	1.225	0.176	44.32	1.647	55.68	1.746
2	1.414	0.301	56.65	1.753	43.35	1.637
3	1.732	0.477	65.56	1.817	34.44	1.537
4	2	0.602	78.89	1.897	21.11	1.324
6	2.449	0.778	83.23	1.920	16.77	1.225
8	2.828	0.903	89.98	1.954	10.02	1.001
12	3.464	1.079	99.74	1.999	0.26	-0.585

Table 7: Regression analysis data of Famotidine sustain release Tablets

Batch	Zero Order	First Order	Higuchi	Peppas
	R^2	R^2	R^2	R^2
F7	0.812	0.903	0.801	0.952

CONCLUSION

Chamoline mucilage was used as a sustained release matrix excipient in the preparation of Famotidine sustained release tablets. The Famotidine tablets were tested, and the results show that as the mucilage concentration increased, drug release was delayed due to an increase in gel strength and the formation of a gel layer with a longer path of diffusion, resulting in a reduction in the drug's diffusion coefficient. As a result, it can be inferred that Chamoline mucilage, which is an effective sustained release matrix forming agent, can be employed to prepare sustained release Famotidine tablets.

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