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FORMULATION, DEVELOPMENT AND EVALUATION OF FAMOTIDINE ORODISPERSIBLE TABLETS

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ABSTRACT

The objective of the present study was to prepare Famotidine as Orodispersible tablets. Orodispersible tablets dissolve rapidly and show higher bioavailability than conventional tablets. Stomach acidity symptoms are treated by many effective drugs; however, they are slow to produce the desirable effect. Therefore, to decrease the patient time in suffering of these symptoms, Orodispersible drug-delivery system significantly increased patient acceptance by virtue of rapid disintegration, self-administration without water and finally improved patient compliance. Famotidine is selective H2 receptor blocker, used in treat duodenal ulcer condition and heartburn. The drug absorbed slowly and incompletely from GIT, bioavailability 40% and onset of action is less than 1hr (Initial; 1hr – 4hr (peak), in order to improve onset of action and increase bioavailability Famotidine was developed as Orodispersible tablets. Tablets were prepared by wet granulation and direct compression methods using sodium starch glycolate and croscarmellose sodium and crospovidone as superdisintegrants. The tablets were evaluated for weight variation, thickness, diameter, hardness, friability, wetting time, *in-vitro* dispersion time, *in-vitro* disintegration time, assay and *in-vitro* dissolution study. Hardness and friability data indicated good mechanical strength of tablets. The results of *in-vitro* disintegration time of F4 and F6 indicated that the tablets dispersed rapidly in mouth within 23.97, 10 seconds and 106.48%, 92.82% of the drug release within 5 minutes respectively. It was concluded that F4 and F6 are the best formulations of Famotidine Orodispersible tablets in order to increase onset of action and bioavailability of drug.

KEYWORDS: Famotidine, Orodispersible tablets, Superdisintegrants, Drug delivery systems.

INTRODUCTION

Most of the oral pharmaceutical dosage forms like conventional tablets and capsules are formulated to be swallowed or chewed. Elderly people and children sometimes have difficulties in swallowing these dosage forms. Such problem is more serious for bedridden patients. This problem is also applicable to active working or travelling people who do not have ready access to water.[1] Recent advances in novel drug delivery system aims to provide rational drug therapy by enhanced safety and efficacy of drug molecule by formulating a convenient dosage form for administration and also by ensuring better patient compliance.[2]

Oral drug delivery has been known as the most widely used route of drug administration when compared to all the other routes that have been explored for delivery of different dosage forms to systemic circulation.[1-5] The reason for such popularity of oral route may be attributed to its ease of administration. Recent advances in novel drug delivery systems (NDDS) aim at formulating a convenient dosage form for administration and to achieve better patient compliance to enhance safety and efficacy of drug molecules.[4-15]

An oral fast dissolving drug delivery system is a novel tablet dosage form, which dissolves or disintegrates in the oral cavity with a good taste and flavor increasing the acceptability of bitter drugs without the need of water or chewing and hence called melt in mouth tablets or Orodispersible or rapid disintegrating or quick dissolving tablets. The drugs may be absorbed from mouth, pharynx or esophagus while the saliva passes down into stomach. Advantages of the fast dissolving tablets include rapid onset of action, ease of swallowing without the aid of water, enhanced dissolution rate, increased gastric absorption, minimized first pass metabolism, improved oral bioavailability and improved patient compliance. ODTs formulation combines the advantages of both conventional tablets and liquid formulations.[5-20]

Solid dosage forms are popular because of low cost, ease of administration, accurate dosage self-medication, pain avoidance, and the most importantly the patient compliance. The most prevalent solid dosage forms are being tablets and capsules. One essential downside of such dosage forms is Dysphagia (trouble in gulping) is basic among all age gatherings. Normal grumblings about the trouble in gulping tablets are size, surface, and taste of tablets. Geriatric and pediatric patients and voyaging patients, who might not have prepared access to water, are most needing simple gulping dosage forms. To satisfy these medicinal needs, pharmaceutical technologists have built up a novel oral dosage form known as Orodispersible tablets (ODTs) which disintegrate quickly in salivation, normally inside only seconds, without the need to take water.[13-43]

Famotidine

The Famotidine IUPAC name: 3-[[2-(diaminomethylideneamino)-1,3-thiazol-4-yl] methylsulfanyl]-N'-sulfamoylpropanimidamide.

Description: Famotidine is a histamine type 2 receptor antagonist (H2 blocker) which is commonly used for treatment of acid-peptic disease and heartburn. It is white to pale yellowish-white, crystalline powder. It is freely soluble in dimethylformamide and glacial acetic acid; slightly soluble in methanol; very slightly soluble in water; practically insoluble in acetone, in alcohol, in chloroform, in ether, and in ethyl acetate. Pharmacokinetic data: The absorption of famotidine is dose-dependent and incomplete absorption. The oral bioavailability ranges from 40-50%, and the Cmax is reached in 1- 4hours post-dosing. While the bioavailability can be slightly increased with the intake of food and decreased by antacids, there is no clinical significance. The steady-state volume of distribution ranges from 1.0 to 1.3 l/kg. It is found in breast milk at the lowest concentrations compared to other H2 receptor antagonists. The protein binding of Famotidine is about 15 to 22%. The metabolism of Famotidine undergoes minimal first-pass metabolism. About 25-30% of the drug is eliminated through hepatic metabolism. The only metabolite identified in humans is the S-oxide. Route of elimination About 65-70% of the total administered dose of Famotidine undergoes renal elimination, and 30-35% of the dose is cleared by metabolism. Following intravenous administration, about 70% of the drug is eliminated in the urine as an unchanged drug. The elimination half-life is about 2 to 4 hours. The renal clearance is 250-450 ml/min, indicating some tubular excretion. Because the renal clearance rate exceeds the glomerular filtration rate, Famotidine is thought to be mainly eliminated via both glomerular filtration and renal tubular secretion.[15-40]

In the present study, it was proposed to formulate Orodispersible tablets of Famotidine by using wet granulation and direct compression technique methods, with the aim of reaching high serum concentration of the drug in a short time period. In this study, effort has been made to formulations the Orodispersible tablets using superdisintegrants like sodium starch glycolate and croscarmellose sodium and crospovidone.

MATERIALS AND METHODS

Famotidine, Sodium Saccharin, Croscarmellose Sodium, Crospovidone. Sodium Starch Glycolate. Mannitol, Aerosil, Magnesium Stearate, Avicel PH101, Avicel PH102, Talc, Sucralose, Raspberry, Sodium Lauryl Sulfate and Lycatab were gift from (Shephaco Pharmaceutical Industry Company-Yemen).

Preparation of Powder Blends for Compression of Famotidine Formulations

Formulations (F1-F4) each tablet containing 20 mg Famotidine were prepared by wet granulation method using the ingredients given in Table 1. Four formulations were prepared using pure drug Famotidine and three superdisintergrants namely croscarmellose sodium, crospovidone and sodium starch glycolate. The powder blend was mixed with mixture of Lycatab (F1, F3 and F4) or Povidone K30 (F2) and distilled water to obtain a coherent mass. The coherent mass was passed through a 16 mesh to form granules. The wet granules were dried at 60^0C for 1 hour in a hot air oven. After drying, the granules were passed through 22 mesh and the granules were evaluated for mass-volume relationship. Then the granules were mixed with magnesium stearate. Then the lubricated granules were compressed into tablets weighing 200mg using rotary tablet compression machine of punch size 8mm to produce convex faced tablets with a hardness of 3-4 kg/cm^2. The compressed tablets were evaluated for various tablet properties. Compatibility studies were carried out between Famotidine and commonly used tablet excipients in the performulation stage.

Formulations (F5- F12) each tablet containing 20mg Famotidine were prepared by direct compression method using different ingredients. Various batches of tablet formulations prepared are shown in Table 1. Optimum combination was worked out based on powder blend properties and disintegration time of the tablets.

Table 1: Ingredients Used in The Preparation of Famotidine Formulations ODTs.

Ingredients	Quantity Per Tablet (mg)											
	Formulation Code											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Famotidine	20	20	20	20	20	20	20	20	20	20	20	20
Sodium Starch Glycolate	16	10	16	16	12	12	12	12	12	12	----	12
Croscarmellose Sodium	10	----	10	----	----	----	----	---	----	7.5	7.5	----
Avicel PH 101	105.6	47	86	88	----	----	---	----	----	----	----	----
Avicel PH 102	----	----	----	----	88	----	90.5	59	57	51.5	56	54.5
Mannitol	29	99	45	45	----	88.5	----	30	35	40	40	40
Crospovidone	----	8	----	10	6	6	6	7.5	6	----	7.5	6
Aerosil	2	2	2	2	1	1	1	1	1.5	1	1	1
Talc	2	----	1	1	1.5	1	1	1	1.5	----	1.5	1.5
Povidone K 30	----	4	----	----	----	----	----	----	----	----	----	6
Sodium Saccharin	1.4	----	----	----	----	----	----	----	----	----	----	----
Sucralose	----	2	2	2	5	5	5	1.5	2	3	3	3
Raspberry	2	2	2	2	3	3	3	1.5	1.5	1.5	1.5	1.5
Sodium Lauryl Sulfate	----	4	4	2	2	2	----	----	2	2	2	3
Mg Stearate	2	2	2	2	1.5	1.5	1.5	1.5	1.5	1.5	----	1.5
Lycatab	10	-----	10	10	10	10	10	15	10	10	10	----
Total	**200**	**200**	**200**	**200**	**150**	**150**	**150**	**150**	**150**	**150**	**150**	**150**

Evaluation of Orodispersible Tablets of Famotidine[28-40]

Weight Variation

The weight variation test would be satisfactory method of determining the drug content uniformity. Twenty tablets randomly were taken from each batch and weighted individually, calculating the average weight, and comparing the individual tablet weights to the average. The average weight of one tablet was calculated.

Diameter Test

The diameter test one of tests which used for determination of the tablets size, it is done by taking five tablets from each batch randomly. Diameter may obtain by using suitable micrometer.

Thickness Test

The thickness test of five tablets were picked from each batch randomly and thickness was measured individually using "Vernier- caliper" (Electronic Digital Caliper). It is expressed in millimeter and average was calculated.

Hardness Test

The hardness test or tablet crushing strength. The force required to break a tablet in a diametric compression was measured using digital tablet hardness tester. It is expressed in kg/cm^2. Five tablets were randomly selected from each batch and hardness of tablets was determined by using digital hardness tester. The mean values and standard deviation for each batch were calculated.

Friability Test

The friability test is performed to assess the effect of friction and shocks, which may often cause tablet to chip, cap or break. Roche friabilator was used for the purpose. Pre-weighed sample of five tablets from each batch were placed in the friabilator, which was then operated for 100 revolutions. After 100 revolutions the tablets were dusted and reweighed. Compressed tablets should not lose more than 1% of their weighed.

***In-vitro* Disintegration Time**

The *in-vitro* disintegration time was determined using disintegration test apparatus. A tablet was placed in each of the six tubes of the apparatus and one disc was added to each tube. The time in seconds taken for complete disintegration of the tablet with no palatable mass remaining in the apparatus was measured in seconds.

Wetting Time

The wetting time of the tablets was measured using a simple procedure. Circular tissue paper of 10cm diameter were placed in a petri dish with a 10cm diameter. 10ml of distilled water containing a yellow water- soluble dye (sunset dye), were poured into the tissue paper placed in the petri dish. A tablet was placed carefully on the surface of the tissue paper. The time required for the solution to reach upper surface of the tablet was noted as the wetting time.

***In-vitro* Dispersion Time**

The in-vitro dispersion time this test is performed to ensure disintegration of tablets in the salivary fluid. Tablet was added to 10 ml of phosphate buffer solution pH 6.8 (pH of saliva). Time required for complete dispersion of tablet was measured. Three tablets from each batch were randomly selected and *in-vitro* dispersion time was performed.

Assay of Famotidine ODTs

The assay of Famotidine ODTs in phosphate buffer (pH 6.8) by UV Spectrophotometer method to determine the percentage of active ingredient in the tablet according to

the range of Pharmacopeia. Five tablets from each batch were weighed and powdered 20mg equivalent weight of Famotidine in tablet powder was accurately weighed and dissolved in 100 ml of phosphate buffer (pH 6.8) in a 100 ml of volumetric flask to obtain a stock solution, sonication for one hour, filtered, diluted suitably and analyzed for drug content at 265nm using UV-Visible Spectrophotometer.[33-40]

***In-vitro* Dissolution Studies of Famotidine ODTs**

The *in-vitro* drug release was determined by estimating the dissolution profile. USP II Paddle apparatus was used and paddle was allowed to rotate at 50 rpm. Phosphate buffer (pH 6.8) 900 ml was used as a dissolution medium at 37±0.5°C temperature. Determination of amount of drug dissolved form tablets was carried by UV Spectrophotometer at 265 nm. In this test, six tablets from each batch was used for the studies. At specified time intervals (5, 10, 15), 5 ml of samples were collected and immediately replaced with an equal volume of fresh medium. Samples were analyzed by using UV Spectrophotometer at 265 nm using phosphate buffer as blank.

RESULTS AND DISCUSSION

Table 2: Evaluation of Post Compression Parameters of Famotidine Formulations ODTs.

Formulae. No	Average Weight(mg)±S.D	Thickness (mm)	Diameter (mm) ± S.D	Friability %	Hardness Kg/cm^2
F1	213.61±16.02	4.32 ± 0.22	8.19±0.41	0.04	4.34
F2	214.53 ± 16.84	4.60±0.23	8.17±0.41	0.65	3.06
F3	206.79 ± 15.51	4.28 ± 0.21	8.41±0.42	1	5.19
F4	202.07 ± 15.15	4.40 ± 0.22	8.45±0.42	0.25	2.84
F5	150.13 ± 11.26	3.10 ± 0.16	8.41±0.42	0.09	3.27
F6	147.26 ± 11.04	3.05 ± 0.15	8.42±0.42	0.31	4.84
F7	152.88 ± 11.47	3.23 ± 1.16	8.18 ± 0.41	0.07	4.87
F8	150.63 ± 11.30	3.14 ± 0.16	8.16 ± 0.41	0.25	4.42
F9	148.75 ± 11.16	3.09 ± 0.15	8.15 ± 0.41	0.05	5.0
F10	146.81 ± 11.01	3.12 ± 0.16	8.15 ± 0.41	0.42	3.24
F11	149.84 ± 11.24	3.25 ± 0.16	8.19 ± 0.41	0.25	4.36
F12	143.01 ± 10.73	3.06 ± 0.15	8.16 ± 0.41	0.03	4.32

Table 3: Evaluation of Post Compression Parameters of Famotidine Formulations ODTs.

Formulae. No	(Sec)*In-Vitro* Disintegration Time	Wetting Time (Sec)	*In -Vitro* Dispersion Time (Sec)
F1	55.71	25.39	74.61
F2	94.60	141.10	229.33
F3	123.39	59.16	202.75
F4	23.97	42.77	20.33
F5	11	12.52	40
F6	10	38.29	55
F7	9.33	9.49	26.66
F8	22.33	23.88	36.66
F9	24.14	35.12	48.33
F10	19	104.07	86.33
F11	19.17	35.08	31.66
F12	50.42	164.72	89.33

In this study, Famotidine ODTs were prepared and evaluated for achievement of fast action of active pharmaceutical agent. After compression of ODTs were evaluated for their quality control parameter (thickness, diameter, weight variation, hardness, friability, disintegration time, dissolution test, wetting time, and dispersion time) the results are shown in Tables 2 and 3.

The weight variation parameter of formulations F1 to F4 was found to be (202.07-214.53 mg) while formulations F5 to F12 was observed between (143.01-152.88 mg) which were well within the acceptable limit for uncoated tablets as British Pharmacopeia (B.P) and United State Pharmacopeia (USP). The thickness parameter of formulations F1 to F4 was found to be (4.28 - 4.596 mm) while in formulations F5 to F12 was found to be (3.048 - 3.252 mm), all values of the formulae were within the acceptable range.

The diameter of the tablets was found in the range (8.15 - 8.45mm) all the formulations possessed uniform diameter the results are shown in Table 2. The hardness of tablets was determined and was found to be in the range (2.84 - 5.19 kg/cm^2) for formulations (F1 to F4). While in formulations (F5 to F12) it was found to be in the range (3.24 - 5 kg/cm^2) which are satisfactory strength to withstand the applied mechanical shocks. The friability of all formulations was found to be not more

than 1%, which indicates tablets' ability to withstand abrasion in handling and packaging.

The results of disintegration time of Famotidine ODTs were found to be (23.97 - 123.39 sec) in formulations with tablet size 200mg. While disintegration time were found to be (9.33 - 50.42 sec) in formulations with tablet size 150mg.

The *in-vitro* wetting time was also studied to know the time required for complete wetting of tablets when placed on tongue. The *in-vitro* wetting time of all formula were varying between (25.39 - 141.1 sec) for the formulations F1, F2, F3 and F4 while other formulations between (9.49 - 164.72 sec). The dispersion time was found to be (20.33 - 229.33 sec) in which it is characterized by relatively higher values in formulations F1 to F4 than F5 to F12 that was found to be (26.66 - 89.33 sec).

Assay of Famotidine ODTs

The assay of Famotidine ODTs (F1 - F4) were found in the range (108.81 - 112.63 %) and (F5 - F12) were found in the range (90.14 - 95.52 %). The acceptable limit of Famotidine content as per tablet USP is (90 - 110 %). The results revealed that the assay of Famotidine was within the acceptable limits except F1 is upper the acceptable range the results are shown in Table 4.

Table 4: Results of Assay of Famotidine ODTs in Phosphate Buffer (pH 6.8) By UV-Visible Spectrophotometer Method.

Formulae. No	Average Weight(g)	Absorbance(nm)	Content %
F1	0.2032	0.5197	112.63
F2	0.2142	0.5152	110.75
F3	0.2041	0.5142	110.53
F4	0.2040	0.5062	108.81
F5	0.1492	0.3872	91.48
F6	0.1484	0.3958	91.47
F7	0.1552	0.3918	90.55
F8	0.1529	0.4058	93.78
F9	0.1503	0.4133	95.52
F10	0.1495	0.4043	93.44
F11	0.1484	0.4114	95.08
F12	0.1464	0.3814	90.14

***In-vitro* Dissolution Studies**

Table 5: Percentage of Drug Release of Famotidine Formulations ODTs.

Formulae. No	% Drug Release		
	5 min	10 min	15 min
F1	103.28 %	106.10 %	108.09 %
F2	102.73 %	103.05 %	104.09 %
F3	92.87 %	98.44 %	99.63 %
F4	106.48 %	106.91 %	107.95 %
F5	88.89 %	89.89 %	90.92 %
F6	92.82 %	93.13 %	95.40 %
F7	89.46 %	93.77 %	93.80 %
F8	92.28 %	92.76 %	93.62 %
F9	81.95 %	85.88 %	87.85 %
F10	91.19 %	92.71 %	93.37 %
F11	83.03 %	91.55 %	93.94 %
F12	89.16 %	91.24 %	92.32 %

The in-vitro dissolution profile of Famotidine is one of the most important experiments to prove if the ODTs are convenient to be used for rapid action. This study was applied to all formulations by using in phosphate buffer (pH 6.8) at time interval (5, 10, 15 minutes) digital dissolution tester at (37± 0.5°C).

The results of percentage of dissolved active ingredient, Famotidine, are tabulated in Table 5. The results of formulations prepared by wet granulation with tablet size 200mg have shown that the drug release of F4 was found to be 106.48% at 5 minutes. In addition, the drug release of F1 and F2 were found to be 103.28%, 102.73% while the drug release of F3 was found to be 92.87 % at 5 minutes. The Results of formulations prepared by direct compression with tablet size 150mg have shown that the drug release of F6 was found to be 92.82 % at 5 minutes. When compared to drug release F8, F10 were found to be 92.28 % and 91.19% while the drug release of F9 was found to be 81.95 % at 5 minutes and the rest formulations drug release were gradually increased with increasing the time of dissolution.

From the above results and discussion, it was concluded that formulation of Orodispersible tablets of Famotidine containing sodium starch glycolate and crospovidone i.e. F4 and F6 can be taken as an optimized formulation of Orodispersible tablets for drug release 106.48 % and 92.28 % release within 5 minutes. The present study shows that the dissolution rate of Famotidine can be enhanced through the great extent by addition of superdisintegrant methods. The rapid drug dissolution might be due to easy breakdown of the particles due to porous structure formation after superdisintegration addition method and rapid absorption of drugs into the dissolution medium.

CONCLUSION

Orodispersible tablets of Famotidine were prepared by wet granulation and direct compression methods using sodium starch glycolate, croscarmellose sodium and crospovidone as superdisintegrants. The tablets disintegrated rapidly in oral cavity and had acceptable hardness and friability. The *in-vitro* drug release from the tablets shows significantly improved drug dissolution. Hence it could be concluded that the superdisintegrant based Orodispersible tablets of Famotidine would be quite effective in providing quick onset of action without need for water for swallowing or administration. In order to improve onset of action and increase bioavailability Famotidine was developed as Orodispersible tablets. The results of *in-vitro* disintegration time of F4 and F6 was found to be 23.97, 10 seconds and the drug release 106.48%, 92.82% at 5 minutes respectively indicated that the tablets dispersed rapidly in the mouth. It was concluded that F4 and F6 are the best formulations of Famotidine Orodispersible tablets in order to increase onset of action and bioavailability of drug.

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