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FORMULATION AND EVALUATION OF MOUTH DISSOLVING FAMOTIDINE TABLET

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Abstract: Difficulty in swallowing (dysphagia) is common among all age groups, especially in elderly and pediatrics. Mouth dissolving tablets constitute an innovative dosage forms that overcome the problems of swallowing and provides a quick onset of action. The purpose of this study was to formulate and evaluate mouth dissolving tablet of famotidine using croscarmellose sodium and sodium starch glycolate as a superdisintegrant. Tablets were prepared by wet granulation technique. The granules were evaluated for angle of repose, bulk density, tapped density, bulkiness, compressibility index and hausners ratio. The tablets were evaluated for hardness, uniformity of weight, friability, wetting time, water absorption ratio, disintegration time and dispersion time. *In vitro* release studies were performed using Disso-2000 (paddle method) in 900ml of pH 6.8 at 50rpm. The optimum formulation was subjected for stability studies and the chosen formulation was found to be stable.

Keywords: Famotidine, croscarmellose sodium, sodium starch glycolate, mouth dissolving tablets.

Introduction

Famotidine is a H_2 receptor antagonist[1]. A thiazole ring containing H_2 blocker which binds tightly to H_2 receptors and exhibits longer duration of action despite a elimination[2]. Famotidine after oral administration has an onset of effect within 1 hr and inhibition of gastric secretion is present for the next 10-12 hrs[3]. Elimination is by renal and metabolic route. It is therefore important to decrease the dose of the drug for patient with kidney or renal failure[1, 3]. Famotidine not only decrease both basal, food-stimulated acid secretion by 90% or more but also promote healing of duodenal ulcer[4,5].

Many patients find it difficult to swallow tablets and hard gelatin capsules and do not take their medicines as prescribed. The concept of mouth dissolving drug delivery system emerged from the desire to provide patient with more conventional means of taking their medications. Mouth dissolving tablets (MDT) disintegrate and are dissolving rapidly in the saliva with out the need of water.

Disintegrants plays a major role in the disintegration and dissolution of MDT. Superdisintegrants provide quick disintegration due to combined effect of swelling and water absorption. Due to swelling of superdisintegrants, the wetted surface of the carrier increases, this promotes the wettability and dispersibility of the system thus enhancing the disintegration and dissolution[6].

Materials and Methods

Materials

Famotidine and CrosCarmellose Sodium (CCS) was a gift sample from Orchid Pharmaceuticals, Chennai. Sodium Starch Glycolate (SSG) and mannitol were obtained from S-d-fine chem. Mumbai. Microcrystalline cellulose, Aspartame and magnesium stearate were purchased from Loba chemie Mumbai. Isopropyl alcohol was obtained from Nice chemicals, Cochin. All other ingredients used were of analytical grade.

Preparation of famotidine tablets

Tablets were prepared by wet granulation method using the ingredients given in Table 1. Nine formulations were prepared using two super disintegrants namely croscarmellose sodium and sodium starch glycolate. Tenth formulation was prepared without superdisintegrants. The powder blend was mixed with

isopropyl alcohol to obtain a coherent mass. The coherent mass was passed through a 16 mesh to form granules. The wet granules were dried at 60^0 C for 1 hour in a hot air oven. After drying, the granules were passed through 22 mesh and the granules were evaluated for the flow properties. Then the granules were mixed with magnesium stearate. Then the lubricated granules were compressed into tablets weighing 200mg using 6mm round flat faced punches in a rotary tablet press (Rimek mini press-1, Model RSB-4, Karnavathi Engineering, Ahmedabad) to a hardness of 3-4 kg/cm^2. The compressed tablets were dedusted and evaluated for various tablet properties.

Evaluation of Granules

Angle of repose

Angle of repose (θ) was determined using fixed funnel method. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely onto the surface[7]. The diameter of the granular cone was measured and angle of repose was calculated using the following equation.

$$\theta = \tan^{-1} (h/r)$$

Where h and r are the height and radius of the cone.

Bulk Density

Bulk density is the ratio between a mass of granules and its bulk volume[7,8]. It is expressed by gm/cc.

Bulk Density = Weight of granules/ Bulk volume

Tapped Density

Tapped density is the ratio between mass of granules and volume of the granules after tapping[7, 9]. It is expressed by gm/cc.

Tapped Density = Weight of granules/ Tapped volume

Bulkiness

Reciprocal of bulk density is known as bulkiness[10]. It is expressed by cc/gm.

Bulkiness= 1/ Bulk density

Compressibility index and hausner ratio

The compressibility index and the closely related hausner ratio have become the simple, fast and popular methods of predicting powder flow characteristics. The compressibility index and hausner ratio were determined by measuring both the bulk density and tapped density of granules[7].

Compressibility Index = Bulk density – Tapped density× 100 / Tapped density

Hausner ratio = Bulk density/ Tapped density

Evaluation of tablets

Hardness

The strength of tablet is expressed as tensile strength (kg/cm^2). The tablet crushing load, which is the force required to break a tablet by compression[11]. It was measured using a tablet hardness tester (Pfizer Hardness Tester).

Weight variation

Twenty tablets were randomly selected and individually weighed (Scaltec digital balance). The average weight of the selected tablets was calculated[7].

Friability

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. Preweighed sample of ten tablets 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 loose more than 1% of their weigh[7].

Percentage friability = (initial weight-final weight/initial weight) × 100

Disintegration Time

The test was carried out on six tablets using distilled water at 37^0C $\pm$ 2^0C was used as disintegration media and the time in second taken for complete disintegration of the tablet with no palable mass remaining in the apparatus was measured in seconds[12].

Wetting time

Five circular tissue paper of 10cm diameter were placed in a petridish with a 10cm diameter. 10 ml of simulated saliva pH (phosphate buffer pH 6.8) was poured into the tissue paper placed in the petridish. Few drops of eosin solution were added to the petridish. 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[12, 13].

Water absorption ratio

The weight of the tablet before keeping in the petridish was noted (W_b). Fully wetted tablet from the petridish was taken and reweighed (W_a) [13]. The water absorption ratio R can be determined according to the following formula.

$R = (W_a - W_b)/W_a \times 100$

Estimation of drug content

Ten tablets from each formulation were powdered. The powder equivalent to 100mg of famotidine was weighed and dissolved in phosphate buffer pH 6.8 in 100ml standard flasks. From this suitable dilution was prepared and the solution was analyzed at 265nm using UV double beam spectrophotometer (Elico SL164) using pH 6.8 as blank[14].

Evaluation of taste by panel

The taste evaluation was done by panel testing. For panel testing 20 healthy human volunteers were selected. Then the selected panel of 20 healthy human volunteers was requested to taste all the formulations by keeping in the mouth till they disintegrated and rank it on a scale of perception ranging from 0-5[15].

FT-IR studies

Infrared spectrum was taken for the pure famotidine, CCS 5%, SSG 5% and for the F-9 formulation. FT-IR studies were obtained by KBR disk method using computer-mediated Fourier transformed infrared spectroscopy (FTIR) (Shimadzu). It was used to find out the drug-carrier interactions.

***In vitro* release studies**

In vitro drug release study was carried out using Disso-2000 dissolution apparatus (paddle type). Dissolution medium 900ml of pH 6.8 was placed into the dissolution flask maintaining the temperature at $37^{o} \pm 0.5^{o}$C and rpm of 50. Samples measuring 10ml were withdrawn every 1min intervals, replace same quantity of fresh dissolution medium. Collected samples were suitably diluted with pH 6.8 and analyzed at 265nm using pH 6.8 as blank in UV-double beam spectrophotometer.

Stability studies

Short-term stability studies on the optimum formulation (F-9) were carried out by storing the tablets (in amber colored rubber stoppered vials) at 40^{0}/75% RH for 3 weeks. At every 1 week intervals, the tablets were examined for physical changes, properties, drug content and *in vitro* release studies[16].

Results and Discussion

Mouth dissolving tablets of famotidine was prepared by wet granulation method using cross carmellose sodium and sodium starch glycolate as a super disintegrant and microcrystalline cellulose as a diluent. Mannitol serves as sweetening agent helps in the masking bitter taste of the drug. Total ten formulations were designed including without superdisintegrant.

The formulated granules were evaluated and the results are shown in the table 2. The angle of repose was in the range of 31.66 $\pm$ 0.56 to 32.58 $\pm$ 1.12 indicating good flow property. The bulk density and tapped density was in the range of 0.3151 $\pm$ 0.0252 to 0.3974 $\pm$ 0.0176 gm/cc and 0.4178 $\pm$ 0.0248 to 0.4651 $\pm$ 0.0354 gm/cc. The bulkiness was in the range of 2.52 $\pm$ 0.11 to 2.72 $\pm$ 0.11 cc/gm. The compressibility index and hausner ratio was in the range of 11.88 $\pm$ 3.84 to 15.21 $\pm$ 5.52% and 1.14 $\pm$ 0.06 to 1.18 $\pm$ 0.08 indicating good flow property.

The compressed tablets were evaluated for physical properties and the results are tabulated in table 3. The hardness was in the range of 3.54 $\pm$ 0.23 to 3.88 $\pm$ 0.18 kg/cm^2. Uniformity of weight was found to be in the range of 192.25 $\pm$ 0.004 to 202.30 $\pm$ 0.004 mg. The friability of all the formulation was within 1% which was in the range of 0.37 $\pm$ 0.05 to 0.55 $\pm$ 0.18%. The wetting time for all the formulated tables was in the range of 23.6 $\pm$ 1.82 to 161.4 $\pm$ 2.41 sec. The water absorption ratio was found to be in the range of 61.74 $\pm$ 3.03 to 190.86 $\pm$ 4.75 %. The disintegration time of all the formulated tablets between 14.8 $\pm$ 0.84 to 135 $\pm$ 1.58 sec. The *in vitro* dispersion time for F-1 to F-10 formulation was found to be in the range of 31.0 $\pm$ 0.71 to 212.6 $\pm$ 1.14 sec. The drug content was in the range of 97.72 $\pm$ 0.74 to 101.12 $\pm$ 0.33%. The result for the evaluation of taste by panel was shown in table 4. All the 20 volunteers reported the taste of the tablet as sweet. It showed that the bitter taste of the drug can be masked by the followed procedure.

The IR spectra revealed that the drug is compatible with the superdisintegrants and other excipients. The IR spectrum of F-9 formulation showed that all the characteristics peak of famotidine pure drug, thus conforming that no interaction of drug occurred with the component of the formulation.

F-3, F-6 and F-9 formulations were selected for the *in vitro* release studies because the disintegration time for these three formulations was within a minute. The *in vitro* release study for the formulations F-3, F-6 and F-9 were shown in the figure 1. The *in vitro* release study shows that about 96% and 98% of drug was released in F-3 and F-6 formulations in 4 min. But in F-9 formulation 98% of drug was released within 3 min. It indicates that the combination of cross carmellose sodium and sodium starch glycolate increase the drug release.

F-9 formulation was selected for the short term stability study. F-9 formulation was placed in 40^{0}/75% RH for 3 weeks. Every 1 week intervals the tablets are evaluated for all the physical parameters, drug content and *in vitro* release studies. There was no significant changes were found when the values are compared with 0 day of formulation.

Conclusion

The release of drug from the F-9 formulation was quick when compared to F-3 and F-6 formulation. It shows that the combined effect of cross carmellose sodium and sodium starch glycolate gives synergistic effect. Undoubtedly the availability of various technologies and the manifold advantages of MDT will surely enhance the patient compliance, low dosing, rapid onset of action, increased bioavailability, low side effect, good stability and its popularity in near future.

Table 1: Formulation of famotidine mouth dissolving tablets

Ingredients (mg)	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9	F-10
Famotidine	20	20	20	20	20	20	20	20	20	20
Croscarmellose sodium	2	6	10	-	-	-	-	-	-	-
Sodium starch glycolate	-	-	-	2	6	10	-	-	-	-
Croscarmellose sodium + Sodium starch glycolate	-	-	-	-	-	-	2	6	10	-
Microcrystalline cellulose	106	102	98	106	102	98	106	102	98	108
Mannitol	60	60	60	60	60	60	60	60	60	60
Aspartame	8	8	8	8	8	8	8	8	8	8
Isopropyl alcohol	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Magnesium stearate	4	4	4	4	4	4	4	4	4	4
Menthol	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Total weight	200	200	200	200	200	200	200	200	200	200

Table 2: Evaluation of prepared famotidine granules

Formulation code	Angle of repose (θ)	Bulk density (gm/cc)	Tapped density (gm/cc)	Bulkiness (cc/gm)	Compressibility index (%)	Hausner ratio
F-1	31.97 ± 0.53	0.3800 ± 0.0247	0.4421 ± 0.0436	2.56 ± 0.17	13.88 ± 3.56	1.16 ± 0.05
F-2	32.09 ± 0.65	0.3974 ± 0.0176	0.4651 ± 0.0354	2.52 ± 0.11	14.36 ± 3.78	1.17 ± 0.05
F-3	32.58 ± 1.12	0.3681 ± 0.0151	0.4178 ± 0.0248	2.64 ± 0.17	11.88 ± 3.84	1.15 ± 0.05
F-4	32.07 ± 0.79	0.3745 ± 0.0264	0.4436 ± 0.0531	2.68 ± 0.18	15.21 ± 5.52	1.18 ± 0.08
F-5	32.15 ± 0.92	0.3736 ± 0.0151	0.4409 ± 0.0369	2.68 ± 0.11	14.95 ± 5.47	1.18 ± 0.08
F-6	32.45 ± 1.27	0.3736 ± 0.0151	0.3974 ± 0.0176	2.68 ± 0.11	15.09 ± 4.95	1.18 ± 0.07
F-7	32.50 ± 0.62	0.3910 ± 0.0144	0.4485 ± 0.0344	2.56 ± 0.09	12.56 ± 4.47	1.14 ± 0.06
F-8	31.66 ± 0.56	0.3681 ± 0.0151	0.4318 ± 0.0207	2.72 ± 0.11	14.73 ± 0.59	1.17 ± 0.01
F-9	32.12 ± 0.95	0.3151 ± 0.0252	0.4576 ± 0.0417	2.56 ± 0.17	14.14 ± 3.73	1.17 ± 0.05
F-10	32.21 ± 0.67	0.3681 ± 0.0151	0.4330 ± 0.0316	2.72 ± 0.11	14.84 ± 4.88	1.16 ± 0.08

All the readings are expressed as mean ± standard deviation (n=5)

Table 3: Evaluation of prepared famotidine mouth dissolving tablets

Formulation code	Hardness[a] (kg/cm^2)	Uniformity of weight[b] (mg)	Friability[c] (%)	Wetting time[a] (sec)	Water absorption ratio[a] (%)	Disintegration time[a] (sec)	Dispersion time[a] (sec)	Drug content[c] (%)
F-1	3.72 ± 0.11	194.60 ± 0.005	0.55 ± 0.18	111.6 ± 2.70	75.28 ± 2.18	101.4 ± 1.52	143.6 ± 1.52	98.88 ± 0.44
F-2	3.76 ± 0.09	199.95 ± 0.006	0.55 ± 0.14	80.8 ± 2.39	123.67 ± 1.86	73.4 ± 2.70	97.6 ± 0.89	98.20 ± 0.66
F-3	3.72 ± 0.11	200.55 ± 0.006	0.45 ± 0.10	44 ± 1.58	134.26 ± 2.23	39.5 ± 1.14	56.2 ± 0.84	99.52 ± 0.33
F-4	3.60 ± 0.14	193.25 ± 0.006	0.44 ± 0.11	106 ± 1.22	82.64 ± 6.94	97.6 ± 1.14	122 ± 2.12	98.32 ± 0.72
F-5	3.64 ± 0.22	195.75 ± 0.006	0.43 ± 0.11	75.8 ± 1.30	123.82 ± 1.26	71.6 ± 0.55	89.8 ± 1.30	97.72 ± 0.74
F-6	3.84 ± 0.17	197.00 ± 0.003	0.40 ± 0.12	39.6 ± 1.52	146.99 ± 4.83	35.8 ± 1.30	46.4 ± 0.55	100.24 ± 0.46
F-7	3.88 ± 0.18	192.25 ± 0.004	0.37 ± 0.05	85.2 ± 3.19	134.26 ± 2.23	80.8 ± 0.84	112.8 ± 1.92	98.94 ± 0.65
F-8	3.54 ± 0.23	201.95 ± 0.003	0.38 ± 0.09	68.4 ± 1.52	180.56 ± 3.32	67.2 ± 1.79	77.6 ± 1.67	98.31 ± 0.77
F-9	3.84 ± 0.17	202.30 ± 0.004	0.42 ± 0.08	23.6 ± 1.82	190.86 ± 4.75	14.8 ± 0.84	31.0 ± 0.71	101.12 ± 0.33
F-10	3.80 ± 0.24	197.65 ± 0.005	0.42 ± 0.10	161.4 ± 2.41	61.74 ± 3.03	135 ± 1.58	212.6 ± 1.14	99.04 ± 0.67

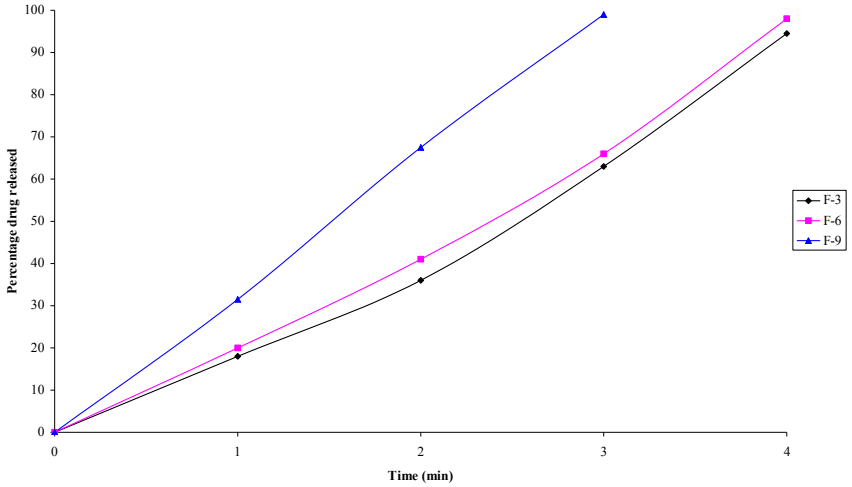
Where a = 5, b=20, c=10,
All the readings are expressed in average of five determinations

Table 4: Evaluation of taste by the panel

Formulations	No. of volunteers rating the preparation as*					
	0	1	2	3	4	5
F-1 to F-10	20					

0* = Good, 1= Tasteless, 2= Slightly bitter, 3= Bitter, 4= Very bitter, 5= awful

Figure 1: Comparison of *in vitro* release study of F-3, F-6 and F-9 formulations



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