Pharmacovigilance

Banala et al., J Pharmacovigil 2015, 3:5
http://dx.doi.org/10.4172/2329-6887.1000179

Research Open Access

Design and Evaluation of Floating Multi Unit Mini Tablets (MUMTS) Muco Adhesive Drug Delivery System of Famotidine to Treat Upper Gastro Intestinal Ulcers

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Received date: September 11, 2015; **Accepted date:** October 05, 2015; **Published date:** October 12, 2015

Abstract

Ulcer is one of the most common evaluated diseases caused by many reasons like, *H. pylori* bacteria infection, over secretion of acid levels in the stomach, irregular formation of mucosa and some of the NSAIDs treatment. Famotidine is a H_2 receptor antagonist, used to reduce the gastric acid secretion in the stomach. The aim of the present investigation was the development and evaluation of famotidine multi-unit tablet encapsulated system to treat upper gastro intestinal ulcers.

The drug release was controlled with matrix polymers like POLYOXWSR 1105 and HPMC K_4M. The tablets were prepared by direct compression technique. The prepared tablets were evaluated for physico chemical parameters like weight variation, hardness, friability, buoyancy studies, drug content, *in vitro* dissolution and mucoadhesive property in porcine gastric mucosa. Further, the intra gastric behaviour of optimized formulation was evaluated in human volunteers under fasting conditions. All the parameters of prepared tablets were within the acceptable limits as per USP. The optimized formulation exhibited floating lag time of 10 ± 2 sec with total floating time of 12 h and *in vitro* release profile of 99.14 ± 3.21% in 12 h. The mucoadhesion time was found to be visually >12 h in ph 6.8 phosphate buffer. *In vivo* radiographic imaging studies revealed that the mean residence time of single mini tablet in stomach was found to be 8h in healthy human volunteers.

Abbreviations

MUMTS: Multi Unit Mini Tablets; HPMC: Hydroxy Propyl Methyl Cellulose; POLYOX WSR: Poly Ethylene Oxide Water Soluble Resin

Introduction

Famotidine is the Histamine H2 receptor antagonist used to treat peptic ulcers disease by reducing gastric acid secretion in the stomach. Basically famotidine is propanamide derivative (Figure1).

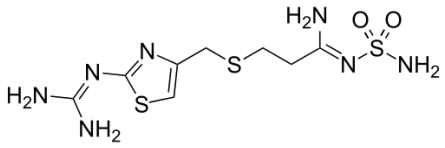

Figure 1: Chemical formula of famotidine.

Famotidine shows the effect on histamine [1], which stimulates cells in the stomach (parietal cells) to produce acid. It inhibits the action of histamine on the parietal cells, thus reducing the production of acid and famotidine was introduced into the market in the year of 1986 [2]. Later in 1999, orally disintegrating tablets were available in the market and generic preparation was available in the year of 2001 [3]. Till now the research is looking to develop a new strategy for better activity. Example, recently in 2015 UK was developed a chewable tablet of an antacid combination with famotidine.

This has shown better action compare with famotidine alone. Hence, in this present work we attempt to develop famotidine floating multi-unit mini tablet (MUMT) muco adhesive strategy for the improvement of tablet retention time in the stomach followed with the adhesion to gastric mucosa. This strategy was developed based on the reported solubility and which is a class IV drug having the poorly water soluble property, but it has shown pH dependent solubility and highly soluble in 0.1 N HCl and poorly soluble in alkaline pH [4].

The method of delivery was achieved with the multi-unit particulate system by encapsulated into the HPMC capsule. The advantages of this system includes: reduces the risk from local irritation and toxicity, predictable bioavailability, reduce the dose dumping; minimize the drug fluctuation in the plasma and high dose also easy to administer [5].

Materials and Methods

Famotidine was a kind gift sample from Dr. Reddy's laboratory, Hyderabad, India, Avicel pH 102, HPMC K_4M and POLYOX WSR were purchased from Sigma Aldrich (Mumbai, India), Sodium bicarbonate purchased from SD fine chemicals, Mumbai, India. Talc and magnesium stearate were purchased from Merck Pvt. Ltd., Mumbai, India. All other chemicals used were of analytical grade.

Preparation of floating-mucoadhesive MUMTS

MUMTS were prepared by using direct compression technique. In this method of preparation, all the excipients were triturated in to a

mortar and pestle then it was transferred in to the poly bag and mixed for 15 min, finally talc and magnesium stearate was added to that blend. The final powder blend carried out for the pre-compression evaluation parameters like (angle of repose, Hausner's ratio and compressibility index).

Then it was introduced for the compression. The compression was done by multi stationary rotary compression machine (Riddhi, Ahmadabad, India) with 3 mm flatted punches. The composition of tablets is shown in Table 1.

Ingredients (mg)	F1	F2	F3	F4	F5	F6
Famotidine	40	40	40	40	40	40
NaHCO3	20	20	20	20	20	20
HPMC K_4M	25	30	35	-	-	-
POLYOX WSR 1105	-	-	-	15	20	25
Avicel pH 101	47	48	37	57	52	47
Talc	4	4	4	4	4	4
Mg. stearate	4	4	4	4	4	4
Total wt.	140	140	140	140	140	140

Table 1: Composition of MUMTS.

Drug and excipients compatibility study by differential scanning calorimetry

DSC analysis was carried out utilizing a Perkin-Elmer Diamond DSC instrument (DSC4000, Perkin Elmer, USA). To evaluate any possible drug interaction with the employed excipients and thermal characteristics of the individual additives used in the formulation. Samples of 3-5 mg of pure drug and optimized formulation were weighed and sealed separately in crimped aluminium pans. The samples were heated at a temperature of 20°C/min under nitrogen purge [6].

Evaluation parameters of MUMTS

All the prepared tablets were evaluated for hardness (n=6) was determined by the Mansanto hardness tester, thickness (n=6) was determined with vernier callipers, friability (n=20) was tested with Roche friabilator and weight (n=10) test were performed with randomly selected tablets then % weight variation was calculated.

Drug content estimation

Randomly collected 20 tablets were triturated in a mortar and equivalent weight of the powder was taken in a beaker containing 100 mL 0.1 N HCl, followed by stirring for 30 min then the solution was passed through the 0.45 µm size filter and absorbance was measured at 286 nm by UV visible spectrophometer (Systronics-117, Hyderabad, India).

In vitro buoyancy **studies:** All the formulations were carried out for the *in vitro buoyancy* study, according to the method described by Rosa et al. [7]. The tablets were introduced into the beaker containing 0.1 N HCl.

The time taken for the tablet to rise to the surface and float was taken as floating lag time (FLT). The duration of time floated on surface is called as total floating time (TFT).

In vitro **release study:** The *in vitro* study was carried out with USP type II dissolution apparatus with 50 rpm at 37°C and the basket containing 900 mL of 0.1 N HCl was used as dissolution medium.

About 5 mL of sample were collected at predetermined time intervals for up to 12h and again replaced with 5 mL fresh medium. The results were analysed with UV-visible spectroscopy (systronics-117, Hyderabad, India).

Ex vivo **residence studies:** The *ex vivo* residence study was determined with porcine stomach mucosa. The mucosa was isolated from the porcine stomach and that was tied to the glassslide 2.2*7 cm size. The tablet was kept in to the middle of the slide and pressed for 1 min time with a drop of pH 6.8 phosphate buffer for providing wetting property to the tablet.

Then the tablet was introduced in to the beaker containing 500 mL of pH 6.8 phosphate buffer in presence of little agitation by magnetic stirrer at 25 rpm. The study was carried out for the 12 h time period [8].

In vivo **radio graphic study:** The *in vivo* radio graphic study was performed with single mini tablet containing radio opaque substance (Barium sulphate 10% w/w)) for clear visualization as per Table 2, which were replaced with drug.

The radio graphic images were taken for every 1 h of the time period. Then study was conformed that the total in vivo residence time in the stomach [9].

S.No	Ingredient	F5
1	Famotidine	5
2	$BaSO_4$	5
3	$NaHCO_3$	5
4	POLYOX WSR 1105	4
5	MCC 101	13
6	Talc and mg stearate	2+2

Table 2: Composition of famotidine tablet for radio graphic study.

Results and Discussion

Drug excipients compatibility studies by differential scanning calorimetry

DSC thermograms of pure drug and optimized formulation are shown in Figure 2. The DSC thermogram of famotidine showed sharp endothermic peak at 166.70°C and it was corresponding to famotidine reported melting point of 165 to 170°C.

In case of optimized formulation (F5), the drug peak was preserved with slight shift in the melting point. Hence, there was no significant change was noticed from the melting point and indicated that no interaction between drug and excipients.

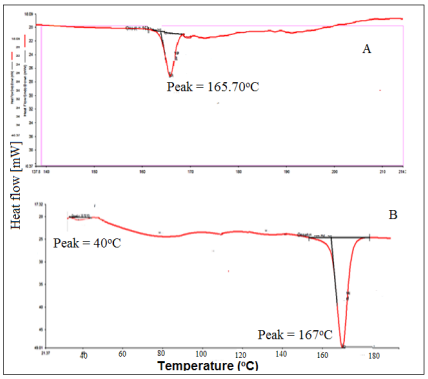

Figure 2: DSC thermograms of A) Pure drug and B) Optimized formulation (F5).

Pre compression evaluation parameters

From the results, pre-compression parameters of the powder blend were within the pharmacopoeial specifications (Table 3).

Formulation	CI	Angle of repose	Hausner's ratio
F1	12.3	28.6o	1.16
F2	11.2	28.8o	1.13
F3	12.6	27.5o	1.04
F4	12.4	29o	1.02
F5	11	27	1.00
F6	11.5	30	1.09

Table 3: Pre-compression evaluation parameters.

Compressibility index was shown good (12-16) the angle of repose value has suggested good flow property (25-30) and Hausner's ratio values in the range 1.2-1.5, indicates free flowing nature of material. The post compression parameters express the satisfactory results. The results suggested uniformity of the tablets were good and within the limits (Table 4).

Post compression evaluation parameters

Formulation Code	Thickness (mm)	Hardness (Kg/cm^2)	Weight variation (mg)	Friability (%)	Drug content (%)
F1	1.75 ± 0.04	4.7 ± 0.02	34 ± 1.2	0.6 ± 0.04	101.43 ± 1.98
F2	1.77 ± 0.06	4.6 ± 0.04	33 ± 1	0.5 ± 0.07	99.5 ± 0.94
F3	1.75 ± 0.02	4.8 ± 0.09	34 ± 1.2	0.4 ± 0.04	100.04 ± 1.33
F4	1.73 ± 0.01	4.4 ± 0.05	34 ± 1.1	0.51 ± 0.04	98.12 ±1 .02
F5	1.69 ± 0.03	4.5 ± 0.04	35 ± 1.5	0.42 ± 0.01	100.3 ± 1.33
F6	1.70 ± 0.05	4.5 ± 0.06	35 ± 0.91	0.3 ± 0.04	101.1 ± 0.78

Table 4: Post-compression evaluation parameters.

In vitro floating buoyancy study

In vitro buoyancy studies were performed to all the formulations. The floating lag time of all the formulations were noticed within the10-15 sec (Table 5). The total floating time of the all formulations were resulted >12, except F1 and F4 formulation.

Formulation code	Floating Lag time (sec)	Total floating time (h)
F1	09	8h
F2	12	>12
F3	13	>12
F4	08	6 h
F5	10	>12
F6	09	>12

Table 5: *In vitro* floating buoyancy results.

Ex-vivo retention time

Ex-vivo study of optimized formulation was conducted in pH 6.8 phosphate buffer in the study results concluded that the F5 and F6 formulation having the greater bio adhesion property because which are prepared with matrix forming high viscus rapid gelling agent, easily cross linked with mucus layer. So, the ratio of polymer increase retention time will be increased (Table 6) [6].

Formulation code	*Ex-vivo* retention time (h)
F1	6 h
F2	6.5
F3	7
F4	6 h
F5	>12
F6	>12

Table 6: *Ex-vivo* retention time results.

In vitro release studies

In vitro release studies were performed in 0.1 N HCl. From the results, formulation F5 was shown 99.14 ± 3.21% release profile within 12 h time period, which is prepared with POLYOX WSR 1105 (Figure 3). F2 has shown 93.24 ± 1.9% within 12 h time period prepared with HPMC K4M. But, formulation F5 has shown better results than the F2 formulation. Hence, it was considered as optimized formulation and used for the further studies.

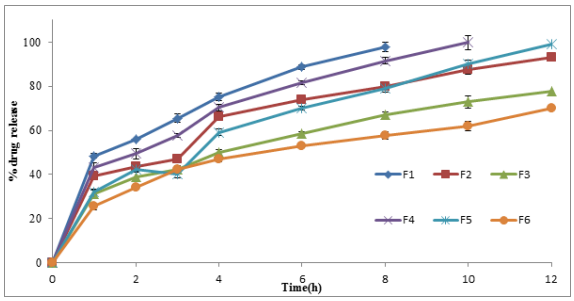

Figure 3: *In vitro* comparative release profile.

In vivo radiographic study

In vivo radio graphic study was conducted in the healthy human volunteers (n=2). The snaps were taken for every 1 h. The mean residence time of floating mini tablets were found to be 8 h (Figure 4).

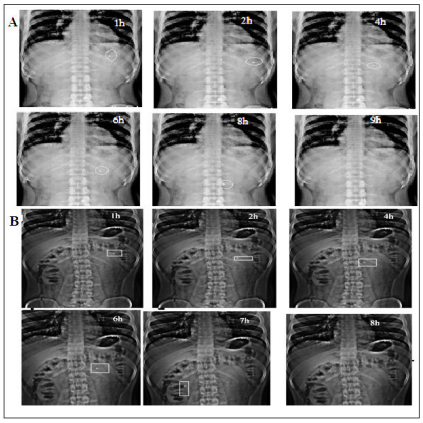

Figure 4: *In vivo* radio graphic images of famotidine floating muco-adhesive mini tablets in healthy human volunteers.

Conclusion

Famotidine MUMTS were prepared successfully by using two different polymers (POLYOX WSR and HPMC K_4M). The optimized formulation was satisfying all evaluation parameters and the results floating Lag time <1 min and total floating time was >12 h. The invitro release was performed with 0.1 N HCl.

The release profile was achieved with 99.14% in 12 h time period. *Ex vivo* retention time was found >12 h and the tablet were found 8 h in the in vivo radiographic study. As a result the polymers effect on the release rate as the polymer increase the release rate was decreased and also both the polymers having bio adhesion property, as a results HPMC K_4M had lesser bio adhesion property compare with the POLYOX WSR, as the ratio of POLYOX increased and the bio adhesion property was increased.

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