

FORMULATION AND *IN VITRO* EVALUATION OF FAMOTIDINE FLOATING TABLETS BY LIPID SOLID DISPERSION SPRAY DRYING TECHNIQUE

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ABSTRACT

The purpose of this investigation was to prepare a gastro retentive drug delivery system of famotidine tablets. Floating tablets of famotidine were prepared employing lipid solid dispersion spray drying technique with gelucire 50/13 and compritol 888 along with HPMC K100M, lactose, sodium bicarbonate and citric acid. The floating tablets were evaluated for uniformity of weight, hardness, friability, drug content, *in vitro* buoyancy and dissolution studies. The effect of release enhancer on drug release profile and floating properties were investigated. The prepared tablets exhibited satisfactory physico-chemical characteristics. Formulation containing gelucire 50/13 and compritol 888 with HPMC K100M (FT5 & FT8) showed good results in *in vitro* buoyancy, but formulation containing gelucire 50/13 and compritol 888 alone failed to float. Increase in the HPMC K100M level was found to increase the floating time of the tablets. From the results it was concluded that famotidine loaded lipid solid dispersion floating tablets prepared by spray drying method is efficient technique for gastro retentive dosage form.

Keywords: Famotidine, floating tablets, *in vitro* buoyancy, lipid solid dispersion.

INTRODUCTION

The present research was focused to develop famotidine loaded lipid solid dispersion floating tablets by spray drying technique. Development of oral controlled release systems has been a challenge to formulation scientists because of the difficulty in localizing the system in target areas of the gastrointestinal tract¹. In recent years, per oral dosage forms for gastric retention have attracted more and more attention for their theoretical advantage in gaining control over the time and the site of drug release. Gastric retention has received significant interest in the past few decades as most of the conventional oral delivery systems have shown some limitations related to fast gastric emptying time². A gastro retentive dosage form (GRDF) can overcome this problem and is particularly useful for drugs that are primarily

absorbed in the duodenum and upper jejunum segments. GRDF technology is one of the promising approach for enhancing the bioavailability and controlled delivery of drugs that exhibit narrow absorption window³. These drug delivery systems have been shown to possess better efficacy in controlling the release rate for drugs with site specific absorption⁴.

Famotidine (FD) is a histamine H₂ receptor antagonist which is widely prescribed in gastric ulcers, duodenal ulcers, Zollinger-Ellison syndrome and gastro esophageal reflux diseases. This drug completely antagonises the parietal cell H₂ receptor. It inhibits histamine, gastrin and acetylcholine stimulated acid secretion; pepsin secretion also falls with the reduction in volume of gastric juice. It increases the incidence and rate of healing of peptic ulcers⁵.

The lipid excipients such as compritol 888 (glyceryl dibehenate), gelucire 50/13 (polyglycolized glycerides), swelling as well as a release-retarding polymer HPMC K100M, gas generating agents such as sodium bicarbonate and citric acid were used in the formulation. Lipid excipients along with HPMC K100M in floating tablets of famotidine would increase the bioavailability, thereby improving the therapeutic efficacy and patient compliance.

MATERIALS AND METHODS

Materials

Famotidine was received as a gift sample from Alembic Limited (Vadodara, India); Gelucire 50/13 (Stearoyl macroglycerides) and glyceryl dibehenate (Compritol 888), were received as gifts from Gateefosse (Mumbai, India); Hydroxypropyl methylcellulose (HPMC K100M) was supplied by Colorcon Asia Pvt Ltd (Goa, India); sodium bicarbonate and lactose were purchased from Laser Chemicals (Ahmedabad, India). Magnesium stearate was purchased from Apex Chemicals (Ahmedabad, India). All other ingredients used were of analytical grade.

Experimental Methods

Preparation of Floating Tablets of Famotidine

The composition of different formulations of famotidine floating tablets was shown in Table 1. The ingredients were weighed accurately and mixed thoroughly. The drug famotidine was dispersed in the lipid matrix consisting of compritol and gelucire at a proportionate ratio. The drug dispersed lipid matrix was dissolved in methanol and obtained a clear solution. The lipid and drug dispersed solution was fed into a spray drier (Labultima, Mumbai) with a co-axial nozzle with co current flow. The total concentration of the solution was 5% w/v. The conditions, that are maintained during spray drying are as follows: Inlet temperature 50°C, outlet temperature 40°C, feed rate 3ml/min, atomization pressure 2.5kg/cm² and aspiration of 25m³/h. The dried drug loaded dispersions were collected from drying chamber and cyclones were subjected for further study. HPMC K100M, lactose, magnesium stearate, sodium bicarbonate and citric acid were proportionately mixed sized through 40/60 mesh there by floating tablets containing famotidine were prepared by direct compression technique by compressed on a single punch tablet machine (Cadmach Machinery Ltd., Ahmedabad, India). The weights of all batches were adjusted with talc. The tablets were round and flat with an average diameter of 12.0 ± 0.1 mm and a thickness of 3.2 ± 0.2 mm.

Table 1: composition of different formulations of famotidine floating tablets

Ingredients (mg per tablet)	Formulation							
	FT1	FT2	FT3	FT4	FT5	FT6	FT7	FT8
Famotidine	40	40	40	40	40	40	40	40
Compritol 888	100	-	100	50	50	25	75	50
Gelucire 50/13	-	100	100	50	50	75	25	50
HPMC K100M	-	-	-	50	75	50	50	100
Lactose	50	50	-	-	-	-	-	-
Sodium bicarbonate	50	50	50	50	50	50	50	50
Citric acid	2	2	2	2	2	2	2	2
Magnesium stearate	2	2	2	2	2	2	2	2

IN VITRO EVALUATION

I. Evaluation of granules

The flow properties of granules (before compression) were characterized in terms of angle of repose, Carr's index and Hausner ratio. For determination of angle of repose (θ), the granules were poured through the walls of a funnel, which was fixed at a position such that its lower tip was at a height of exactly

2.0cm above hard surface. The granules were poured till the time when upper tip of the pile surface touched the lower tip of the funnel. The tan-1 of the (height of the pile / radius of its base) gave the angle of repose. Granules were poured gently through a glass funnel into a graduated cylinder cut exactly to 10 ml mark. Excess granules were removed using a spatula and the weight of the cylinder with

pellets required for filling the cylinder volume was calculated. The cylinder was then tapped from a height of 2.0cm until the time when there was no more decrease in the volume. Bulk density (ρ_b) and tapped density (ρ_t) were

calculated. Hausner ratio (HR) and Carr index (IC) were calculated according to the equations given below:

$$IC = (\rho_t - \rho_b) / \rho_t$$

Table 2: Results of flow properties of granules

Formulation Code	Angle of repose (θ)	Bulk density (gm/cm ³)	Tapped density (gm/cm ³)	Hausner ratio (HR)	Carr's index (IC)
FT1	27.050±0.252	0.583± 0.026	0.684±0.061	1.164	0.141
FT2	27.210±0.352	0.564± 0.045	0.692 ±0.075	1.158	0.155
FT3	27.528±0.235	0.624± 0.043	0.660 ±0.057	1.127	0.115
FT4	28.531±0.320	0.605±0.086	0.655±0.083	1.135	0.130
FT5	27.389±0.674	0.592±0.053	0.679 ±0.057	1.167	0.131
FT6	28.564±0.380	0.571± 0.058	0.683± 0.049	1.130	0.113
FT7	28.462±0.351	0.573± 0.048	0.672±0.048	1.098	0.154
FT8	28.588±0.235	0.547±0.053	0.644±0.025	1.114	0.115

II. Evaluation of floating tablets

(i) Tablet thickness and diameter

The thickness of 10 tablets was measured using a micrometer (Moore and Wright Ltd. Britain Tool, Factory Sheffield, UK). The mean thickness and standard deviation (SD) were calculated⁶.

(ii) Weight Variation Test

To study weight variation, 5 tablets of each formulation were weighed using an electronic balance (AW-220, Shimadzu), and the test was performed according to the official method⁶.

(iii) Drug content

Five tablets were weighed individually and powdered. The powder equivalent to average weight of tablets was weighed and drug was extracted in 0.1 N HCl, Drug content of these solutions was analyzed by using HPLC.

(iv) Tablet hardness

The crushing strength (Kg) of 10 individual tablets were determined using Erweka hardness tester (type TB24, Erweka, GmbH, Heusenstamm, Germany).

(v) Friability

Friability is the measure of tablet strength. Roche friabilator was used for testing the

friability. Percent friability (% F) was calculated as follows,

$$\% F = \frac{\text{Initial weight} - \text{final weight}}{\text{Initial weight}} \times 100$$

(vi) Floating behaviour

The *in-vitro* buoyancy was determined by floating lag time. The tablets were placed in a 100 ml beaker containing 0.1 N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time^{7, 8}.

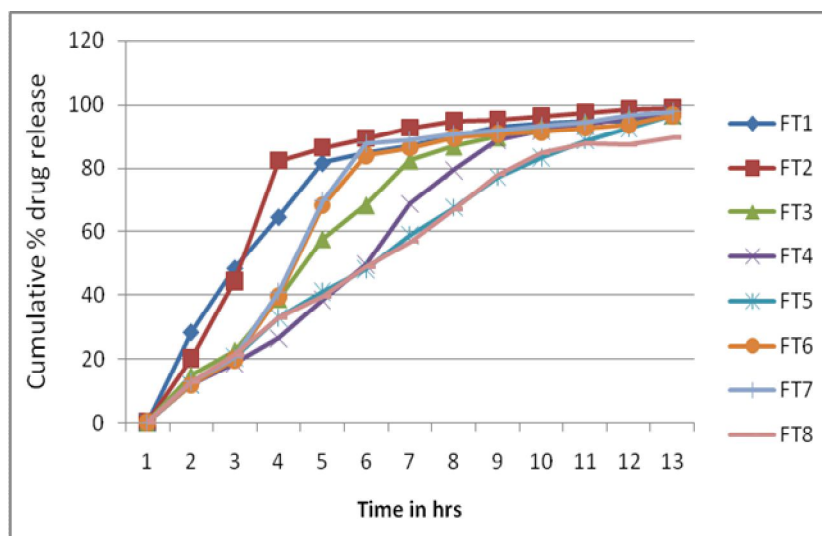
(vii) In Vitro dissolution studies

The release rate of famotidine from floating tablets was determined using United States Pharmacopeia (USP) Dissolution Testing Apparatus type II (paddle method; Veego Scientific, Mumbai, India). The dissolution test was performed using 900 ml of 0.1N hydrochloric acid, at 37 ± 0.5°C and 50 rpm. A sample (10 ml) of the solution was withdrawn from the dissolution apparatus every hourly and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45µ membrane filter and diluted to a suitable concentration with 0.1N hydrochloric acid. Drug content of these solutions was analyzed by using HPLC.

Cumulative percentage drug release was calculated using an equation obtained from a standard curve.

Table 2: Results of physico-chemical characterization of famotidine floating tablets

Formulation Code	Uniformity of weight (mg)	Hardness (kg/cm ²)	Friability (%)	Drug content (mg)	Floating lag time (s)	Total floating time (h)
FT1	300±0.789	6.0±0.165	0.30±0.25	97.46± 0.876	81.57±1.15	2.35±0.03
FT2	299±0.402	6.5±0.333	0.16±0.21	99.56± 0.945	91.57±1.15	3.50±0.05
FT3	298± 0.648	7.16±0.17	0.26±0.04	99.72±0.884	90.53±1.19	8.25±0.06
FT4	299± 0.249	5.01±0.17	0.21±0.13	101.12± 0.678	68.59±3.09	9.25±0.04
FT5	298± 0.228	4.83±0.28	0.32±0.24	99.47± 0.897	39.02±2.40	11.5±0.07
FT6	298± 0.174	5.03±0.44	0.29±0.24	99.87±0.786	57.50±1.70	11.1±0.27
FT7	299±0.684	4.94±0.24	0.32±0.05	97.98±0.975	51.05±2.28	11.4±3.09
FT8	300± 0.278	4.82±0.28	0.31±0.23	101.04± 0.879	34.01±1.65	11.5±0.08

**Fig. 1: *In vitro* dissolution profile of famotidine floating tablets**

DISCUSSION

The floating tablets of famotidine were prepared by lipid solid dispersion spray drying technique using compritol 888, gelucire 50/13, HPMC K100M, sodium bicarbonate and citric acid. The results of the physico-chemical characterization are shown in Table 1.

The granules prepared by spray drying process of solid dispersion were evaluated for their flow properties (Shown in Table No- 2). Angle of repose was in the range of 27.050 to 28.588 with solid dispersion of different formulation. Loose bulk density ranged between 0.571 to 0.624 gm/cm³ and tapped density ranged between 0.644 to 0.692 gm/cm³. Hausner ratio was 1.098 to 1.167 and Carr's index was found to be 0.113 to 0.155. These values indicate that the prepared granules exhibited good flow properties. The weight of the tablet varied between normal limits for different formulations with low standard deviation values, indicating uniformity of weight. The variation in weight was within the range of ±5% complying with pharmacopoeial specifications.

The hardness for different formulations was found to be between 4.82 to 7.16 kg/cm²

indicating satisfactory mechanical strength. The friability was below 1% for all the formulations, which is an indication of good mechanical resistance of the tablet. The drug content varied between 97.46 to 101.12 % w/w in different formulations with low coefficient of variation, indicating content uniformity in the prepared batches. All the tablets were prepared by effervescent approach. Sodium bicarbonate was added as a gas-generating agent. All the batches of tablets were found to exhibit short floating lag times due to presence of sodium bicarbonate and citric acid.

The tablets with swelling as well as a release-retarding polymer HPMC K100M high concentration (FT5 & FT8) exhibited short floating lag time and floated for longer duration as compared with other formulations. In the dissolution of tablet lactose readily dissolve and diffuse out of matrix thus leaving channels or pores in matrix structure from this drug leach out from solid dispersion. Integrity of the tablet decreases and hence, the drug releases from floating tablet containing was quick and sink very fast which fails *in vitro* buoyancy. The t_{80} drug release (fig-1) from floating tablets FT5 & FT8 was found to be 8th hr but in FT1

and FT2 drug release was within 2 to 4 hrs based on the performance of *in vitro* buoyancy and *in vitro* dissolution profile FT5 & FT8 were subjected for further studies.

CONCLUSION

In conclusion a single unit, floating drug delivery system has been developed, which is based on simple lipids such as compritol 888, gelucire 50/13 with HPMC K100M. It's *in vitro* floating performance and the ability to control drug release over prolonged periods of times have been demonstrated. The drug release patterns can effectively be adjusted by varying sample formulation parameters, such as the "lipids /swelling as well as a release-retarding polymer" ratio, initial drug loading, tablet thickness and diameter, type of matrix forming polymer, addition of water-soluble and water in-soluble fillers, and the use of polymer blends. Thus, desired release profile adapted was achieved in sustaining the effervescent-based floating drug delivery in gastro retentive dosage form of famotidine.

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