Research Article

FORMULATION AND EVALUATION OF FAMOTIDINE FLOATING MICROSPONGES

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Article Received on: 21/02/16 Revised on: 04/03/16 Approved for publication: 21/03/16

DOI: 10.7897/2230-8407.07440

ABSTRACT

Floating drug delivery system (FDDS) are of particular interest for drugs that are locally active and have narrow absorption window in stomach or upper small intestine, unstable in the intestinal or colonic environment, and exhibit low solubility at high pH values. The Micro sponge Delivery System (MDS) is a patented polymeric system consisting of porous microspheres. These are tiny sponge like spherical particles that consist of a myriad of interconnecting voids within a non-collapsible structure with a large porous surface through which active ingredient are released in a controlled manner. Famotidine floating microsponges are prepared to improve site specific absorption of drug for peptic ulcer treatment. Modified quasi emulsion solvent diffusion method was used to formulate microsponges. Different concentrations of Eudragit S100 and Polyvinyl alcohol were used and the prepared microsponges were evaluated for % entrapment efficiency, % buoyancy and % cumulative drug release. It was found that the % entrapment efficiency was 88.3%, % buoyancy was 76.4% and % cumulative drug release was 86.9% for F6 formulation. This study presents a new approach based on floating ability of microsponges for treatment of ulcer.

Key words: Microsponges, Floating drug delivery, Quasi emulsion solvent diffusion, Buoyancy Cumulative drug release.

INTRODUCTION

Floating systems or Hydrodynamically controlled systems are low-density systems that have sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time¹. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration^{2, 3}. Different approaches have been proposed to retain the dosage form in the stomach including bioadhesive systems⁴, swelling and expanding systems^{5,6}, floating systems⁷ and delayed gastric emptying devices⁸.

Microsponges are highly cross linked, patented, porous, polymeric microspheres that acquire the flexibility to entrap a wide variety of active ingredients that are mostly used for prolonged topical administration and recently for oral administration⁹. Microsponges are designed to deliver a pharmaceutically active ingredient efficiently at minimum dose and also to enhance stability, elegance, flexibility in formulation, reduce side effects and modify drug release profiles¹⁰.

Famotidine is a histamine H₂ receptor antagonist. Chemically 3-[[[(2-aminoiminomethyl)amino-]4-thiazolyl]methyl]thio]-N-(aminosulfonyl)propanimidamide, is used in the treatment of duodenal ulcer, gastric ulcer, stress ulcers and gastritis, Zollinger-Ellison syndrome and gastro oesophageal reflux disease (dose is 20mg twice daily for 6-12 weeks)¹¹. The low bioavailability (40-45%) and short biological half life (2.5-4.0

hours) of Famotidine, following oral administration favours development of controlled release formulation¹².

The present study aims at developing floating microsponges of Famotidine, prepared by Quasi emulsion solvent diffusion method using Eudragit S100 and subjected to different evaluation studies.

Figure 1: Structure of Famotidine

MATERIALS AND METHODS

Materials

Famotidine was obtained as a gift sample from Dr. Reddy's Laboratories Ltd, Hyderabad, India. Eudragit S 100, Poly vinyl alcohol, Dichloromethane, Sodium chloride were obtained from S.D. Fine chemicals, Mumbai.

Methods

Microsponges were prepared by Quassi emulsion solvent diffusion method. In this method the inner organic phase was prepared by dissolving Eudragit S100 (polymer) in dichloromethane (solvent) and the drug was added to the solution by dissolving under ultrasonication. The outer phase was prepared by dissolving polyvinyl alcohol in water. Then the inner phase was added to the outer phase and stirred for 3 hours. Microsponges were separated by filtration and dried in air heated oven at 40°C for 4 hours^{13, 14}.

EVALUATION

Angle of Repose^{15, 16}

The angle of repose was measured by allowing the powders to fall over a graph sheet placed on horizontal surface through a funnel kept at a certain convenient height (about 2 cm). The height of the heap was measured and then circumference of the base of heap was drawn on a graph sheet with the help of a pencil. The radius of the circle obtained was measured. The angle of repose is given as,

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

Bulk Density

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder in to a measuring cylinder and the initial volume was noted. This initial volume is called bulk volume. The powder was tapped 3 times till a constant volume called bulk density was obtained. From this, the bulk density is calculated according to the formula mentioned below. It is expressed in g/ml and is given by

$$P_t = m/v_t$$

Tapped Density

After determining the poured bulk density, weighed quantity of API was taken into a graduated cylinder. Volume occupied by DRUG was noted down. Then the cylinder was subjected to 500, 750 & 1250 taps in tap density tester. According to USP, the blend was subjected for 500 taps. % Volume variation was calculated and subjected for additional 750 taps. % Variation is calculated.

$$P_t = m/v_t$$

Compressibility Index

Weighed API was transferred to 100ml-graduated cylinder and subjected to 500, 750 & 1250 taps in tap density tester. The difference between two taps should be less than 2%. The % of compressibility index calculated using formula

$$I = V_o - V_t / V_o \times 100$$

V_o = bulk volume, V_t = tapped volume

Hausner's Ratio

It is measurement of frictional resistance of the drug. The ideal range should be 1.2 – 1.5. It is the determined by the ratio of tapped density and bulk density.

$$\text{Hausner's ratio} = \rho_t / \rho_d$$

ρ_t = tapped density, ρ_d = bulk density

Particle Size Analysis

Particle size analysis was performed on Microsponges formulation by optical microscope. Stage micrometer and eye

piece micrometer were adjusted and calibration factor was determined. Then microsponges were taken on a slide and size was observed and noted¹⁷.

$$\text{Calibration Factor} = \frac{\text{Eye piece micrometer division}}{\text{stage micrometer division} \times 10}$$

Encapsulation Efficiency

10mg of the Microsponge formulation was weighed and dissolved in 10ml of 0.1N HCl and subjected to ultrasonication for 20min at 25°C then the sample was filtered and analysed at 266nm¹⁸.

$$\% \text{ Encapsulation efficiency} = (A/T) \times 100$$

A = Actual amount of drug present in weighed quantity of microsponges

T = Theoretical amount of drug present in microsponges.

In-vitro Dissolution Study

900ml of 0.1N HCl Buffer was placed in the vessel and the USP apparatus –II (Paddle) was assembled. The medium was allowed to equilibrate to temperature of 37°C ± 0.5°C. Microsponges were placed in the vessel and were operated for 12 hours at 50 rpm. At definite time intervals 5 ml of the receptors fluid was withdrawn, filtered and again 5ml receptor fluid was replaced. Suitable dilutions were done with receptor fluid and analyzed spectrophotometrically at 266 nm using UV-spectrophotometer¹⁹.

Scanning Electron Microscopy (SEM)

The surface characteristics of the pure drug and microsphere formulation were investigated by scanning electron microscope (PW 1729, Philips, Netherlands). Samples were fixed on a brass tub using double sided adhesive tape and were made electrically conductive by coating with a thin layer of gold and SEM images were recorded at 15 Kev accelerating voltage²⁰.

Drug Release Kinetics

The rate and mechanism of drug release was analysed by fitting the dissolution data into several mathematical models, zero-order, first-order, Higuchi and Peppas²¹.

RESULTS AND DISCUSSION

Determination of λ_{max}

The lambda max of the pure drug was determined using double beam UV-Visible spectrophotometer. It was found to be 266nm.

FTIR Analysis

The FTIR spectra of drug and optimized formula formulation were recorded. The characteristic peaks of the optimized formulation followed the same trajectory as that of the drug and excipients alone with minor differences, indicates that there were no drug excipient interactions.

Micromeritic Properties

The powder blends of microsponges were evaluated for their flow properties; the results were shown (table.5.2). Angle of repose was in the range from 24 to 29 which indicates good flow of the powder for all formulations. The values of bulk density were found to be in the range from 0.424 to 0.520 gm/cm³. The tapped density was in the range of 0.53 to 0.62 gm/cm³. the

values indicate that micrometric properties of the microsponges are within the limits and they exhibit good flow properties

Particle Size

The particle size of the microsponges range between 95.3-140.5 μm . Formulation F11 exhibited maximum particle size of 140.5 μm when both Eudragit and PVA were at high levels. The influence of varying PVA at same quantity of Eudragit was observed in the microsponges F1, F5, F9 of mean size 95.3, 101.9, 121.3. Therefore increase in PVA level increases the size.

Scanning Electron Microscopy (SEM)

Scanning electron microscopy shows the porous surface of the microsponges, this makes them effective carrier and provides more surface area for the coating of the surfactant mixture. Coating of the surfactant mixture on the carrier particles could be shown by the SEM images of microsponges.

Entrapment Efficiency

Formulation F2 (90.7%) showed highest entrapment efficiency. The effect of varying PVA at constant Eudragit quantity did not affect the entrapment efficiency. They showed close entrapment efficiency, 82.5%, 80.4% and 79.4%.

In-Vitro Buoyancy

The microsponges formed with high quantity of Eudragit were more buoyant than those formed with less. The microsponges formed with high level of PVA were less dense than those made with low level of PVA. The buoyancy of microparticles increased with decrease in density of microsponges. All the formulations are within the range of 70-84%.

In-Vitro Drug Release

For a given PVA level, the formulations made with low level of Eudragit exhibited high % CDR. F1, F5, F7 93.6%, 95.6% and 97.5%. Keeping PVA constant an increase in the level of Eudragit forms larger microsponges and hence longer path length which the drug has to traverse. An increase in the level of Eudragit resulted in lowering the rate of drug release. Formulation F9 with 97.5% showed the highest release.

Release Kinetics

The in vitro release data was applied to various kinetic models like zero order, first order kinetics, Higuchi's plot and Peppas's plot to predict the drug release kinetic mechanism. The optimised formulation F6 follows zero order release kinetics. The drug release from optimised formulation shows controlled release.

Table 1: Formulation of Famotidine floating microsponges

Formulation	Famotidine (mg)	Eudragit S -100 (mg)	Dichloro methane (ml)	Polyvinyl Alcohol (%)	Sodium Chloride (%)	Distilled water (ml)
F1	100	400	15	0.5	1	100
F2	100	800	15	0.5	1	100
F3	100	1200	15	0.5	1	100
F4	100	1600	15	0.5	1	100
F5	100	400	15	1	1	100
F6	100	800	15	1	1	100
F7	100	1200	15	1	1	100
F8	100	1600	15	1	1	100
F9	100	400	15	1.5	1	100
F10	100	800	15	1.5	1	100
F11	100	1200	15	1.5	1	100
F12	100	1600	15	1.5	1	100

Table 2: Pre-formulation studies for Famotidine floating microsponges

Formulation code	Bulk density (g/ml)	Tapped density (g/ml)	Angle of repose (°)	Compressibility Index (%)	Hausner's ratio
F1	0.44±0.10	0.56±0.01	25.74	20.35±0.02	1.25±0.01
F2	0.42±0.12	0.53±0.01	24.35	10.86±0.12	1.12±0.006
F3	0.48±0.11	0.63±0.20	24.28	24.60±0.02	1.32±0.01
F5	0.47±0.21	0.58±0.06	26.06	18.43±0.01	1.22±0.01
F6	0.46±0.11	0.56±0.08	27.40	16.39±0.02	1.19±0.021
F7	0.46±0.09	0.53±0.02	26.72	14.46±0.03	1.16±0.01
F9	0.45±0.02	0.56±0.06	25.65	20.17±0.01	1.25±0.01
F10	0.50±0.01	0.62±0.04	28.17	20±0.021	1.25±0.02
F11	0.52±0.05	0.55±0.03	29.24	15.45±0.02	1.057±0.01

Table 3: Evaluation of Famotidine floating microsponges

Formulation Code	Particle size (µm)	Entrapment efficiency (%)	Buoyancy (%)
F1	95.3±12.6	82.5±1.3	70.5±2.0
F2	98.7±16.9	90.7±2.3	74.6±2.3
F3	115.0±10.7	85.3±1.2	79.9±2.0
F5	101.9±12.9	80.4±3.2	72.4±1.05
F6	118.2±11.6	88.3±1.4	76.4±2.0
F7	124.7±9.4	84.8±2.0	82.0±1.8
F9	121.3±10.3	79.4±5.1	75.9±1.8
F10	132.9±11.5	87.3±2.5	80.5±2.5
F11	140.5±9.3	83.7±4.2	84.6±2.7

Table 4: Release Kinetic study of optimised formulation

Formulation	Zero order	First order	Higuchi matrix	Peppas plot	'n' Value
F9	0.9981	0.7896	0.9346	0.8689	0.464

Table 5: Stability study data of F9 formulation at 40°C±2°C with 75%RH±5%

S. No.	Months	% Entrapment efficiency
1.	0	79.5%
2.	1	78.6%
3.	2	77.4%
4.	3	77.1%

Figure 1: FTIR of pure Famotidine

Figure 2: FTIR of Optimised formulation

Figure 3: In-vitro release profile Famotidine from floating microsponges (F1-F3)

Figure 4: In-vitro release profile Famotidine from floating microsponges (F5-F7)

Figure 5: In-vitro release profile Famotidine from floating microsponges (F9-F11)

Figure 6: SEM analysis of optimised formulation (100X)

Figure 7: Zero order kinetics of Optimized Formulation F9

Figure 8: Higuchi plot kinetics of Optimized Formulation F9

Figure 9: Peppas plot kinetics of Optimized Formulation F9

Figure 9: First order kinetics of Optimized Formulation F9

CONCLUSION

Drug delivery via polymer systems has been proposed to be the prevailing in the type of controlled drug delivery devices both in present and future. For scientific as well as economic reasons, such delivery systems have potential advantage which include enhanced therapeutic response, predictable rate of release, extent of absorption and improved patient acceptance. The feasibility of microsponges as floating gastro retentive drug delivery system was studied. This study presents a new approach based on floating ability of microsponges to treat ulcers.

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Cite this article as:

Shireesha Charagonda, Ramya Deepthi Puligilla, Madhu Babu Ananthula, Vasudha Bakshi. Formulation and evaluation of famotidine floating microsponges. *Int. Res. J. Pharm.* 2016;7(4):62-67 <http://dx.doi.org/10.7897/2230-8407.07440>

Source of support: Nil, Conflict of interest: None Declared

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