Research Article

J. innov.appl. pharm. Sci, 8[3-S] 2023, 95-100

Journal of Innovations in Applied Pharmaceutical Science [JIAPS]

Content available at: www.saap.org.in ISSN: 2455-5177

FORMULATION AND EVALUATION OF FLOATING CONTROLLED DRUG DELIVERY OF ANTI-ULCER DRUG LOADED MICROBALLOONS

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Article History

Received: 06-10-2023
Revised: 26-10-2023
Accepted: 17-10-2023

Keywords: Floating microballoons, Famotidine, Eudragit RS100, HPMC K100M, Ethyl cellulose, Solvent evaporation method.

Abstract

An attempt has been made to develop floating drug delivery system for improving the drug bioavailability by prolongation of gastric residence time of Famotidine in the stomach. The floating microballoons were prepared using polymer Eudragit RS100, HPMC K100M and Ethyl Cellulose. Famotidine was used as the model drug. Nine formulations (F1 to F9) were prepared by varying the ratio of polymers. The prepared Famotidine loaded micro balloons were characterized for percentage yield, particle size analysis, surface morphology, micromeritic properties, drug entrapment efficiency, buoyancy studies and in-vitro drug release. The formulated micro balloons were free flowing. The micro balloons with Eudragit RS100 showed higher buoyancy when compared with HPMC K100M and Ethyl Cellulose. On the basis of micromeritic properties, particle size, percentage yield, morphology, buoyancy study, drug entrapment, optimum in-vitro drug release and satisfactory release kinetics, formulation F2 was selected as an optimum formulation.

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https://doi.org/10.37022/jiaps.v8i3-S.532

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Introduction

Oral route is the most convenient and extensively used route for drug administration. This route has high patient acceptability, primarily due to easy of administration'. Oral route of administration has been received more attention in the pharmaceutical field because of the more flexibility in the designing of dosage form than drug delivery design for other routes. Most of the oral controlled drug delivery systems rely on diffusion, dissolution or combination of both mechanisms, to release the drug in a controlled manner to the Gastro Intestinal Tract (GIT) and the drug profile data, such as dose, absorption properties and the quantity of drug needed, one can determine the desired release rate of the drug from controlled release dosage form

Drugs that are easily absorbed from the G.IT and having a short half-life are eliminated quickly from the blood circulation. To avoid this problem the oral controlled release formulations have been developed, as these will release the drug slowly into the GIT and maintain a constant drug concentration in the serum for a longer period of time'. More than 50% of drug delivery systems available in the market are oral drug delivery systems. These systems have the obvious advantages of ease of administration and patient acceptance. Ideal systems are not available. Thus, scientists try to develop systems that can be as close to an ideal system as possible. There are certain situations in which gastric retention is not desirable.

Gastroretentive dosage forms (GRDFs) are a drug delivery formulation that is designed to remain in the gastric region for a long period and significantly prolong the gastric retention time (GRT) of drugs [1] This technology has generated enormous attention over the last few decades owing to its potential application to improve the oral delivery of some important drugs. GRDFs prolonged retention in the upper gastrointestinal tract, greatly improve their oral bioavailability and/or their therapeutic outcome. Various techniques were used to encourage gastric retention of an oral dosage form. A significant approach for the treatment of gastric disorders can be achieved by floating drug delivery systems (FDDS)[2]. FDDS have a bulk density less than gastric fluids; they can float on the gastric juice in the stomach; the drug is released slowly at the

desired rate from the system [3]. A number of FDDS involving various technologies have been developed such as single and multiple-unit hydrodynamically balanced systems, single and multiple-unit gas generating systems, hollow microspheres, and raft forming systems

Hollow microspheres/microballoons are considered as one of the most promising buoyant systems [4]. They possess the unique advantages of multiple-unit systems as well as better floating properties because of central hollow space inside the microsphere. The drug release and better floating properties mainly depend on the type of polymer, plasticizer, and the solvents used for formulation. Commonly used polymers such as polycarbonate, cellulose acetate, calcium alginate, Eudragit S, agar and low methoxylated pectin were used in the preparation of hollow microspheres [5]. Hollow microspheres loaded with drugs in their outer polymer shell were prepared by simple solvent evaporation or solvent diffusion evaporation method to prolong the GRT of the dosage form. The microballoons floated continuously over the surface of an acidic dissolution media containing a surfactant for more than 12 hrs.

A peptic ulcer, also known as peptic ulcer disease (PUD), is a distinct breach in the mucosa of the stomach as a result of caustic effects of acid and pepsin in the lumen[4]. Histologically, peptic ulcer is identified as necrosis of the mucosa which produces lesions equal to or greater than 0.5 cm (1/5"). It is the most common ulcer of an area of the gastro intestinal tract that is usually acidic and thus extremely painful. Helicobacter pylori is one of the most common causes of peptic ulcer that colonizes the antral mucosa [5]. The immune system is unable to clear the infection, despite the appearance of antibodies. Thus, the bacterium can cause a chronic active gastritis (type B gastritis), resulting in a defect in the regulation of gastrin production by that part of the stomach, and gastrin secretion can either be increased, or as in most cases, decreased, resulting in hypo or achlorhydria[7]

Famotidine is a histamine H_2-receptor antagonist that inhibits stomach acid production, and it is commonly used in the treatment of peptic ulcer disease (PUD) and gastro esophageal reflux disease (GERD/GORD)[8]. Famotidine has no effect on the cytochrome P450 enzyme system, and does not appear to interact with otherdrugsFamotidine binds competitively to H_2-receptors located on the basolateral membrane of the parietal cell, blocking histamine affects. This competitive inhibition results in reduced basal and nocturnal gastric acid secretion and a reductionin gastric volume, acidity and amount of gastric acid released in response to stimuli including food, caffeine, insulin, betazole, or pentagastrin.

Methods

Famotidine, Ethyl -cellulose, Eudragit RS1OO, HPMC K100M,Light liquid Paraffin, Acetone, Methanol, Dichloromethane, hydrochloric acid were the ingredients used in the formulation Floating micro balloons were prepared by solvent evaporation method using 1000 mg of drug and different proportions of polymers were dissolved or dispersed in a mixture of dichloromethane and acetone (1:1) at room temperature. A solution of Famotidine was introduced to an external medium of light liquid paraffin (50 ml) in a 500 ml of beaker. The whole system was stirred at 1000 using mechanical stirrer equipped with three blade propellers for 3-4 hours3710.5°C to ensure the evaporation of the solvent. The solvent removal leads polymer precipitation at o/w interphase of droplets forming cavity and thus mark them hollow to impart floating property. The prepared microballoons then filtered washed with petroleum ether, air-dried and stored in desiccators.

Formulation Code	Famotidine (mg)	Eudragit RS100 (mg)	HPMC K100M (mg)	Ethyl Cellulose (mg)	Dichloromethane: Acetone (ml)
F1(1:1)	1000	1000	-	-	1:1
F2(1:2)	1000	2000	-	-	1:1
F3(1:3)	1000	3000	-	-	1:1
F4(1:1)	1000	-	1000	-	1:1
F5(1:2)	1000	-	2000	-	1:1
F6(1:3)	1000	-	3000	-	1:1
F7(1:1)	1000	-	-	1000	1:1
F8(1:2)	1000	-	-	2000	1:1
F9(1:3)	1000	-	-	3000	1:1

Determination of Drug-Polymers Compatibility by FTIR Spectroscopy

FTIR spectra help to confirm the identity of the drug and to detect the interaction of the drug with the carriers. I spectroscopy of pure drug and physical mixture of drug with polymers was carried out to check the compatibility between drug and polymers. The IR spectra of drug with polymers were compared with the standard IR spectrum of the pure drug.

Evaluation of Floating Microballoons

Micromeritic Studies

The prepared microballoons are characterized by their micromeritic properties, such as microballoon size, tapped density, Carr's compressibility index, Hausner's ratio and angle of repose.

Bulk Density

The bulk density is defined as the mass of powder divided by bulk volume. The bulk density was calculated by dividing the weight of the samples in grams by the final volume incm.

$$\text{Bulk density} = \frac{\text{Mass of microballoons}}{\text{Volume of microballoons before tapping}}$$

Tapped Density

Rapped density is the volume of powder determined by tapping by using a pasting cylinder containing weighed amount of sample. The cylinder containing own amount of microballoons was tapped for about 1 minute on a tapped density apparatus until it gives constant volume.

$$\text{Tapped density} = \frac{\text{Mass of microballoons}}{\text{Volume of microballoons after tapping}}$$

Carr's Compressibility Index

This is an important property in maintaining uniform weight.

$$\%\ \text{Compressibility Index} = \frac{\text{Tapped density - Bulk density}}{\text{Tapped density}} \times 100$$

Hausner Ratio

A similar index like percentage compressibility index has been defined by Hausner. Values less than 1.25 indicate good flow, whereas greater than 1.25 indicates poor flow.

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Angle of Repose (Θ)

It is essential that an accurate assessment of flow properties be made as early in the development process as possible so that an optimum formulation can be quickly identified. The angle of repose of each powder blend was determined by glass funnel method.

tan Θ = h/rh= height of the pile and, r= radius of the powder cone

Percentage Yield

The measured weight of prepared microballoons was divided by the total amount of all the excipients and drug used in the preparation of the microballoons, which give the total percentage yield of floating microballoons.

$$\% \text{ Yield} = \frac{\text{Actual weight of product} \times 100}{\text{Total weight of excipients and drug}}$$

Particle Size Determination

Microballoon size was determined by using an optical microscope and the mean microballoon size was calculated by measuring 100 particles with the help of a calibrated ocular micrometer.

Morphological Study using SEM"

The morphological study was carried out by Scanning Electron Microscope. Carried out by using JEOL JSM-6390 a scanning microscope

Percentage Drug Entrapment

percentage Drug Entrapment was determined by taking weighed quantity of gisroballoons equivalent to 50 mg of the drug, thoroughly triturated and dispersed in so ml of 0.1 N HCI (pit-1.2) in 50 ml standard flask and stied for 24 hrs using a magnetic stirrer, filtered out and from the filtrate 1 mi was pipetted out and made up 10 10 ml with 0.1 N HCI and analysed spectrophotometrically at 265 nm against 0.1 N HI blank.

$$\% \text{ Drug Entrapment} = \frac{\text{Amount of drug actually present} \times 100}{\text{Theoretical drug load expected}}$$

In vitro Buoyancy Study™,

Microballoons equivalent to 40 mg of Famotidine were dispersed in a simulated gastric buffer pH 1.2 containing Tween 20 (0.02% w/v).The mixture was stirred with a paddle at 100 rpm. After 12 hrs, the floating microballoons and sinking particulate layer were separated by filtration. Particles of both types were dried at 40°C overnight in a desiccator until constant weight was achieved. weight was measured and buoyancy was determined

$$\text{Buoyancy \%} = \frac{W}{(W, + W,) \times 100}$$

W, and Ws are the weight of the floating and settled microballoons

In-vitro Drug Relese Study,

microballoons containing quantity equivalent to 40 mg of Famotidine by using US dissolution apparatus.

Result and Discussion

Determination of Drug-Polymers compatibility by FTIR Spectroscopy FT-IR spectra of the pure drug and the combination spectra of drug with the polymers, all the characteristic peaks of Famotidine were present in the combination spectra as well thus indicating the compatibility of the drug with the polymers used.

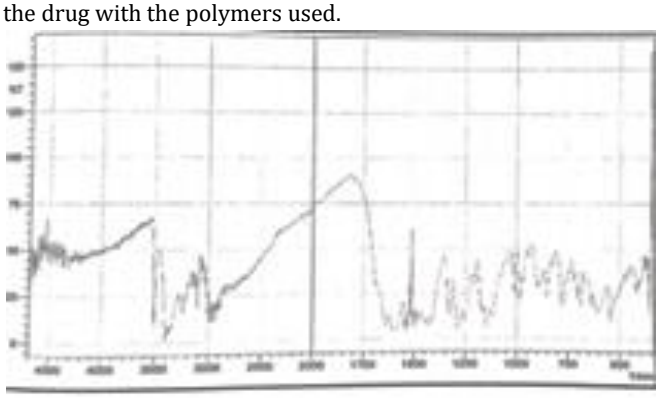


Figure 24: FTIR Spectrum of Famotidine

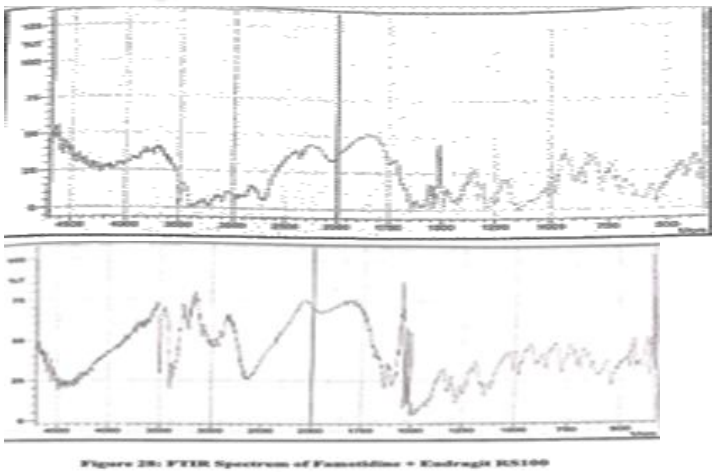


Figure 25: FTIR Spectrum of Famotidine + Eudragit RS100

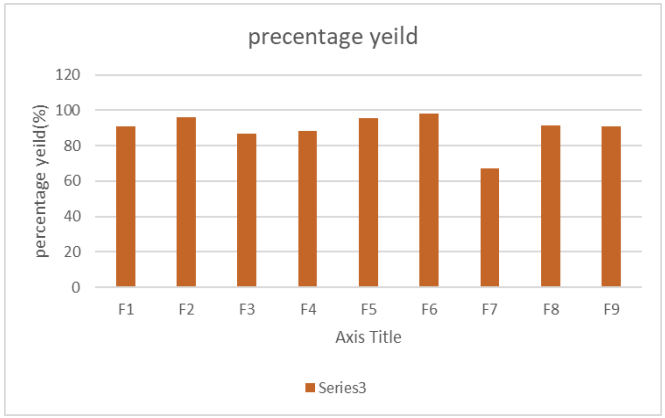
Micromeritic Studies

The results of all formulations F1 to F9 of Floating microballoonsare shown

Formulation code	Bulk density (g/cc)	Tap density (g/cc)	Carr's Index	Hausner ratio	Angle of repose( )
F1	0.425	0.451	5.7650	1.0612	26.27
F2	0.577	0.624	7.5321	1.0815	27.88
F3	0.723	0.772	6.3472	1.0678	29.01
F4	0.372	0.392	5.1020	1.0538	28.34
F5	0.548	0.580	5.5172	1.0584	29.29
F6	0.631	0.673	6.2407	1.0666	30.03
F7	0.728	0.772	5.6994	1.0604	26.37
F8	0.479	0.510	6.0784	1.0647	27.76
F9	0.296	0.316	6.3291	1.0676	28.13

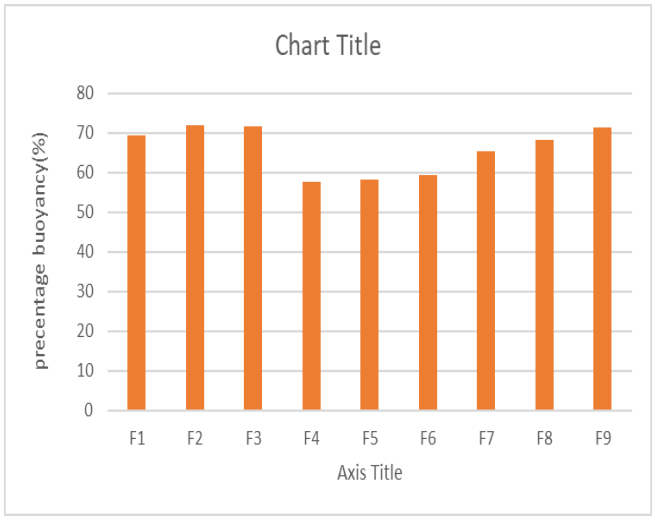
Percentage Yield

The percentage of production yield of the prepared floating microballoons of Famotidine was in the range of 67-98.25% being the highest for formulation F6 and lowest for formulation F7.



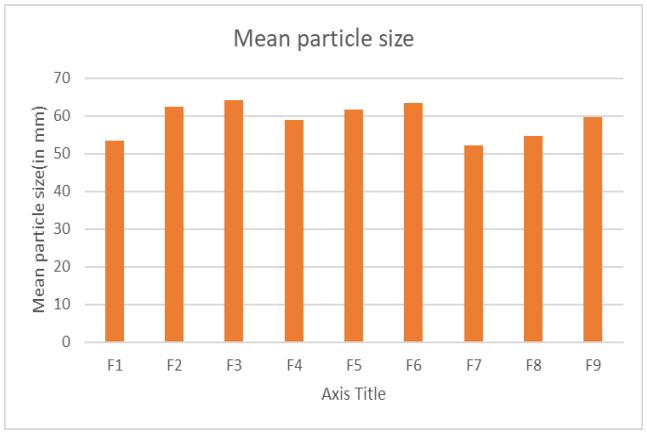
In-vitro Buoyancy Study

The Percentage buoyancy of the prepared floating microballoons of Famotidine was in the range of 57.64-72.01%, being the highest for formulation F2 and lowest for formulation F4



Particle Size Determination

The Mean Particle Size of the prepared floating microballoons of Famotidine was in the range of 52.11-64.21 um being the highest for formulation F3 Famotidine lowest for formulation F7



Morphological Study using SEM

Particle shape and surface morphology had been evaluated using SEM and the prepared microballoons were found to be almost spherical in nature and possessing more or less smooth outer surface.

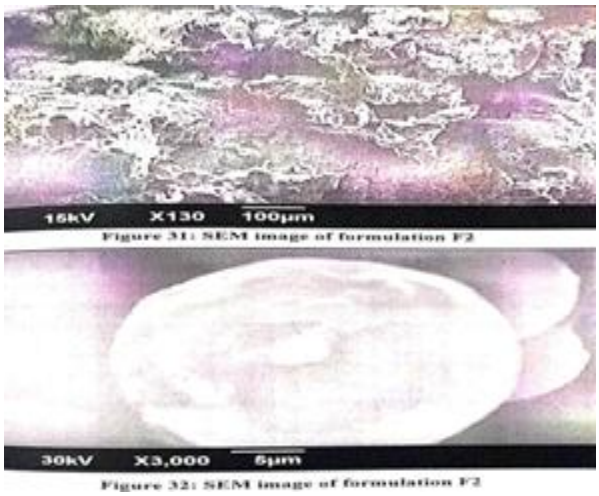
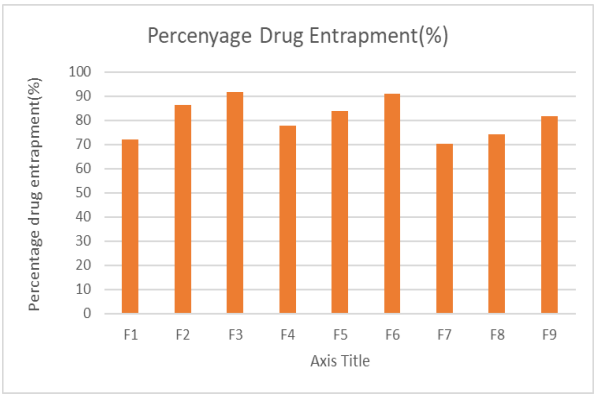


Figure 31: SEM image of formulation F2

Figure 32: SEM image of formulation F2

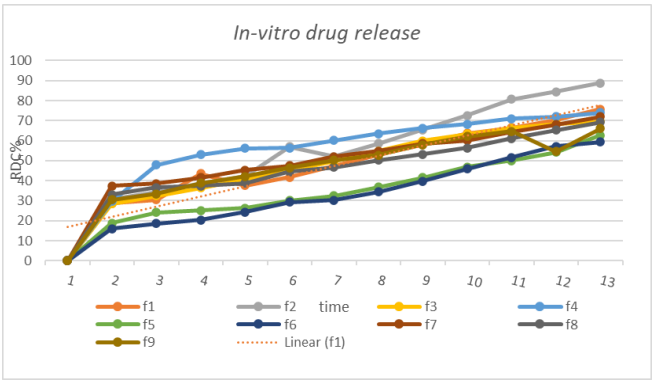
Percentage Drug Entrapment

The Percentage Drug Entrapment of the prepared floating microballoons of Famotidine was in the range of 70.0540-91.7496%, being the highest for formulation F3 owest for formulation F7.



In-vitro Drug Release Study

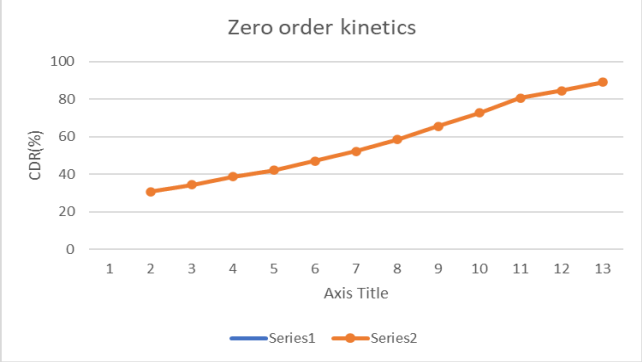
In-vitro release of Famotidine from microballoons was determined by carrying out dissolution test using USP basket method at a stirring rate of 100 pm at temperature. The in-vitro drug release of prepared formulations was found to be sustained in a period of 12 hours and it was highest for formulations containing Budragit R$100(1:2) and lowest for formulations containing HPMC K100M (1:3). The cumulative release of Famotidine significantly decreases with increasing polymer concentration.



Kinetics

The in-vitro drug release data of F2 was applied to various kinetic models like zero order kinetics, first order kinetics, Higuchi plot, Korsmeyer-Peppas plot and Hixson-Crowell plot to predict the drug release kinetics mechanism. The

formulation F2 was best fitted with Higuchi model and it was found to be following Fickian diffusion as release mechanism.



Discussion

The percentage yield obtained in all the formulations was good and in the range of 67-98.25% w/w. The percentage drug entrapment of all the formulations was found good and in the range of 70.0540-91.7496% w/w.[9] The particle size analysis indicated that the size of microballoons was found to increase with increase in the concentration of polymer and range of particle size of the prepared microballoons was found to be 52.11-64.21. The SEM photograph of microballoons revealed that the prepared microballoons were almost spherical with a more or less smooth outer surface**.** Further studies are required to establish the in-vivo bioavailability and in-vitro & in-vivo correlation of bioavailability of the microballoon formulations prepared [10]. This can be used for the further studies of floating microballoons.

Conclusion

Floating is one of the important approaches to the gastric retention of the dosageform. Famotidine with a low oral bioavailability of 40-45% and half-life of 2.5-3.5hours is an example of drugs that could benefit from increased residence in the stomach.

Based on in-vitro buoyancy study and in-vitro drug release characteristics, the formulation F2 was selected as the best formulation, as it showed a percentage buoyancy of 72.01% and a higher in-vitro drug release profile[11] (88.8370% of drug released in 12 hours which was sustained up to 12hours.The in-vitro drug release data of F2 was applied to various kinetic models like zero order kinetics, first order kinetics, Higuchi plot, Korsmeyer-Peppas plot and Hixson-Crowell plot to predict the drug release kinetics mechanism[13].Theformulation F2 was best fitted with Higuchi model and it was found to be following Fickian diffusion as release mechanism.Future scope of floating drug delivery systems lies in the modification techniques of polymer carriers to improve their floating property and to make them more target-specific.Flow properties, suggesting that, in future they could be easily and successfully packed and developed into a capsule dosage form.

The prepared microballoons proved to be a potential candidate as a microparticulate controlled release drug delivery device in this era of patenting novel and controlled release formulations.

Acknowledgement

Not declared

Funding

No

Conflict of interest

No Conflict of interest

Ethical approval and Inform Consent

Not Required

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