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Formulation and evaluation of novel stomach specific floating microspheres bearing famotidine for treatment of gastric ulcer and their radiographic study

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ABSTRACT

Objective: To develop and characterize multiple-unit-type oral floating microsphere of famotidine to prolong gastric residence time and to target stomach ulcer.

Methods: The floating microspheres were prepared by modified solvent evaporation method. Eudragit S-100 was used as polymer. Microspheres were characterized for the micromeritic properties, floating behavior, entrapment efficiency and scanning electron microscopy. The *in-vitro* release studies and floating behavior were studied in simulated gastric fluid at pH 1.2. Different drug release kinetics models were also applied for all the batches. Selected formulations were also subjected for X-ray radiographic study.

Results: Floating microspheres were successfully prepared by modified solvent evaporation technique. Microspheres showed passable flow properties. The maximum yield of microspheres was up to (95.11±0.35)%. On the basis of optical microscopy particle size range was found to be ranging from (52.18±182.00) to (91.64±5.16) μm. Scanning electron microscopy showed their spherical size, perforated smooth surface and a cavity inside microspheres. Microspheres were capable to float up to 20 h in simulated gastric fluid. X-ray radiographic studies also proved its better retention in the stomach.

Conclusions: On the basis of the results, such dosage forms may be a good candidate for stomach targeting and may be dispensed in hard gelatin capsules.

1. Introduction

Oral route of administration is the most convenient and widely used method of drug administration, and the development of stomach specific oral controlled-release drug delivery systems is a challenging job due to the variation of pH in different segments of the gastrointestinal tract, the fluctuation in gastric emptying time and the difficulty of localizing an oral delivery system in a selected region of the gastrointestinal tract. Rapid gastrointestinal transit can prevent the absorption of complete drug in the absorption zone and reduce the efficacy of the administered dose since the majority of drugs are absorbed in stomach or the upper part of small intestine^[1,2].

To overcome the above discussed issues, many types of oral controlled drug delivery systems having prolonged gastric residence times have been reported such as: floating drug dosage systems (FDDS)^[3–7], swelling or expanding system^[8], mucoadhesive systems^[9,10], modified-shape systems^[11], high-density systems and other delayed gastric emptying devices^[12].

FDDS have lower density than gastric fluids and thus remain buoyant in the stomach fluid without affecting the gastric emptying for a prolonged period of time. While the system is floating in the gastric fluid, the drug is released slowly from the system at a desired rate. Materials used for FDDS include carbon dioxide gas-forming agents (carbonate or bicarbonate compounds)^[8,13], highly swellable hydrocolloids and light mineral oils^[14,15]. Multiple unit systems and floating systems prepared by solvent evaporation methods have also been developed^[12,16–20].

However, it has been shown that products based on a multiple unit system comprising many small units have

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advantages over single-unit preparations such as matrix tablets^[21]. The gastric emptying of multiple unit dosage forms occur gradually, in a more consistent manner, with less individual variation^[2,22]. Multiple unit dosage forms also have the potential to distribute widely over a large area in the stomach and small intestine, thus yielding a more predictable drug release by suppressing the effect of many variables in the gastrointestinal environment. As multiple unit dosage forms consist of many small units, less risk of dosage dumping is expected^[23].

Famotidine, a competitive histamine H₂-receptor antagonist is used to treat gastrointestinal disorders such as gastric or duodenal ulcer, gastroesophageal reflux disease, and pathological hypersecretory conditions. Famotidine inhibits many of the isoenzymes of the hepatic CYP450 enzyme system. Other actions of famotidine include an increase in gastric bacterial flora such as nitrate-reducing organisms^[24].

Famotidine is widely used as the treatment of peptic ulcer disease and gastroesophageal reflux disease. Famotidine binds competitively to H₂-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 reduction in gastric volume, acidity, and amount of gastric acid released in response to stimuli including food, caffeine, insulin, betazole and pentagastrin^[25].

Floating microspheres are one of the multiparticulate delivery system and are prepared to obtain prolonged or controlled drug delivery to improve bioavailability and to target drug to specific sites. Microspheres can also offer advantages like limiting fluctuation within therapeutic range, reducing site effects, decreasing dosing frequency and improving patient compliance^[26].

In the present study, the multiple-unit-type oral floating microspheres bearing famotidine were developed by modified solvent evaporation technique. Eudragit S-100 was used as polymer.

The high surface tension of stirring phase causes the solidification and aggregation of polymer on the surface when the polymeric solution is poured from upside. To minimize the contact of polymer solution with interface, a new method of introducing the polymer solution into stirring phase was adopted as established by Lee *et al*^[27].

2. Materials and methods

Famotidine was obtained as a gift sample from Cadila Pharmaceutical Ltd., Mumbai (Maharashtra). Eudragit S100 (Rohm Pharma GmbH, Germany) was used as polymers. All other chemicals and reagents were of analytical grade and were used without further purification.

2.1. Preparation of floating microspheres

Floating microspheres were prepared by the method reported by Kawashima *et al.* with slight modifications^[19]. Ten formulations of floating microspheres were developed. Different ratios of famotidine and Eudragit S-100 were mixed

in a mixture of dichloromethane (DCM) and ethanol (Table 1). The resulting suspension was added slowly into stirring to 0.25% w/v 400 mL solution of polyvinyl alcohol (PVA) at room temperature from the bottom side as shown in Figure 1^[27]. The stirring was continued for 2 h by mechanical stirrer equipped with four blade propellers in order to evaporate the solvent. After evaporation of solvent, microspheres were collected by filtration and washed repeatedly with water. The collected microspheres were dried at room temperature and stored in a desiccator.

Table 1

Batch specifications for floating microspheres.

Code	Drug: polymer (mg)	Speed	Solvent ratio (DCM: ethanol, mL)
FS-1	1:1	900	1:1
FS-2	1:2	900	1:1
FS-3	1:3	900	1:1
FS-4	1:4	900	1:1
FS-5	1:5	900	1:1
FS-6	1:3	1000	1:1
FS-7	1:3	1200	1:1
FS-8	1:3	1300	1:1
FS-9	1:3	900	1:3
FS-10	1:3	900	3:1

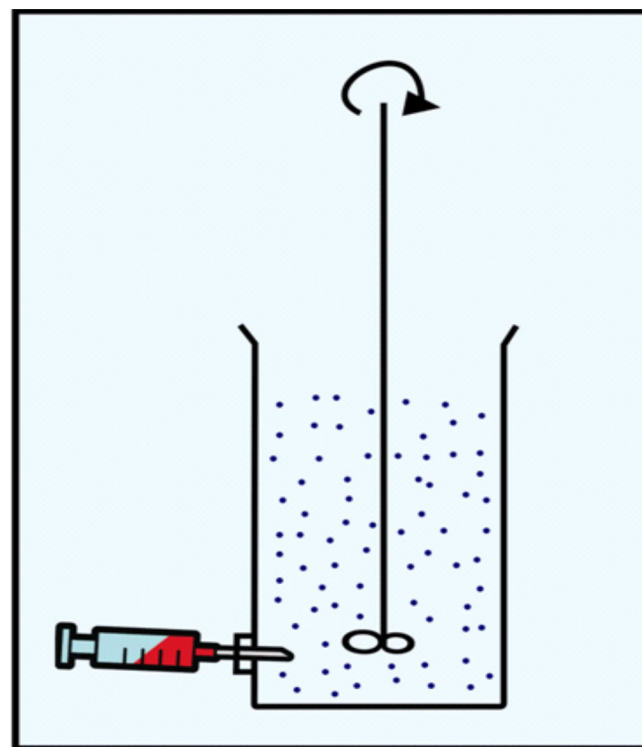


Figure 1. Method of injection of volatile phase into PVA solution.

2.2. Characterization of floating microspheres

2.2.1. Morphology

The morphology of microspheres was studied by scanning electron microscopy (SEM). The samples for SEM were prepared by sprinkling the microspheres on a both side adhesive tape stuck to a stub. Gold palladium coating on the prepared stub was done by using sputter coater (POLARON model SC-76430). The thickness of coating was 200 Å. The coated stubs were randomly scanned under electron microscope (LEO-430, UK). The photomicrograph of prepared microspheres are presented in Figure 2.

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