Development of a floating multiple unit controlled-release system for mosapride

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Floating beads are often used for controlled drug release as they have a gastroretentive property without affecting the gastric emptying rate. In the present study mosapride-controlled release beads were prepared with the help of the ionotropic gelation method, using sodium alginate containing KHCO₃ as the gas-forming agent. The physical characterization of the mosapride beads was examined by SEM. The results showed that the shape and texture of the beads were uniform before and after dissolution. The percentage of mosapride drug entrapment efficiency ranged from 97.4 ± 0.08 to 99.1 ± 0.04. The percentage of mosapride content from the beads was determined by high-performance liquid chromatography (HPLC) and ranged from 97.9 ± 0.08 to 99.6 ± 0.01. The in-vitro percentage release of mosapride from the beads at the end of 14 hours ranged from 90.0 ± 0.2 to 99.5 ± 0.12. The formulated beads in formulations 1 and 3 were sealed in vials and kept for 90 days at 40°C / 75% RH. After 90 days of exposure the percentage drug content was found to be 99.2 ± 0.04. The Floating beads designed for the gastroretentive dosage form could be suitable for controlled drug delivery.

Key words: Gas forming agent, gastric retentive, ionotropic gelation, mosapride-alginate beads

INTRODUCTION

Gastric emptying of dosage forms is an extremely variable process and the ability to prolong and control the emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than the conventional dosage forms. Several difficulties are faced in designing controlled release systems for better absorption and enhanced bioavailability. One such difficulty is the inability to confine the dosage form in the desired area of the gastrointestinal tract. Drug absorption from the gastrointestinal tract is a complex procedure and is subject to many variables. It is widely acknowledged that the extent of gastrointestinal tract drug absorption is related to the contact time with the small intestinal mucosa.[1]

Gastroretentive systems can remain in the gastric region for several hours, and hence, significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves the solubility of drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestines.

Oral controlled release dosage forms have been developed for the past three decades due to their considerable therapeutic advantages.[2] However, this approach has not been suitable for a variety of important drugs characterized by a narrow absorption window in the upper part of the gastrointestinal tract, that is, the stomach and the upper part of the small intestine.[3] Rapid gastrointestinal (GI) transit can prevent complete drug release in the absorption zone and reduce the efficacy of the administered dose, as the majority of drugs are absorbed in the upper part of the gastrointestinal tract (GIT).[4] To overcome these limitations several oral controlled drug delivery systems, with prolonged gastric residence time, have been reported in recent times, such as, Floating Drug Dosage Systems (FDDS),[5] swelling or expanding systems, mucoadhesive systems, modified shape systems, high-density systems, and other delayed gastric emptying devices. Among these systems FDDS have been most commonly used. FDDS have a lower density than gastric fluids and thus remain buoyant in the stomach, without affecting the gastric emptying rate, for a prolonged period of time. While the system is floating in the gastric content, the drug is released slowly from the system at the desired rate.[6]
Mosapride citrate is a 5-HT₄ agonist and its action must be targeted to the esophagus and the upper part of the stomach. Hence, in the present study mosapride citrate loaded floating alginate beads were formulated using the ionotropic gelation method for floating controlled drug delivery. The characterization of the formulated beads, the floating properties, \textit{in-vitro} release studies, and stability of the beads were determined.

\section*{MATERIALS AND METHODS}

\subsection*{Materials}
Sodium alginate (Keltone® HVCR), Hydroxy propyl methyl cellulose [Methocel® E6 premium], Mosapride citrate dihydrate, gift samples obtained from ORCHID HEALTHCARE LTD, Chennai, KHCO₃ AR grade was purchased from S.D Fine Chemicals Ltd., Boissar. All the other chemicals were of analytical grade.

\subsection*{Formulation of floating mosapride beads}
Four different formulations [Table 1] of mosapride alginate beads were tried. 1.6 g mosapride (8\%) was dispersed in 15 ml of water. The resulting dispersion was added to 20 ml of sodium alginate solution (3 and 4\%) containing hydroxy propyl methylcellulose, in the ratio of (sodium alginates : HPMC) 9 : 1 w/w. For controlling the release from the beads, various combinations of hydroxypropyl methylcellulose (HPMC) were tried along with sodium alginate. The, gas-forming agent KHCO₃ was added to the dispersion, with levels starting from 1\% to 20\% w/w. From this, 20 ml of the prepared standard solution, which was shaken on a vortex mixer for one minute. From this, 20 µl volume of internal standard were eluted separately at 5.40 and 2.27 min, respectively [Figure 2]. The eluate was monitored at 270 nm.

\subsection*{Preparation of standard solutions and calibration graph}
Stock solutions of mosapride and internal standard risperidone 1 mg/ml in methanol were prepared. From the stock solution of mosapride, serial dilutions were made with the mobile phase to get concentrations ranging from 50 g, 100 µg, 150 µg, 200 µg, to 250 µg. The linearity of the graph was determined by HPLC. A 100 µl volume of internal standard equivalent to 100 µg of risperidone was added to the prepared standard solution, which was shaken on a vortex mixer for one minute. From this, 20 µl was injected into a HPLC system and eluted with a mobile phase at a flow rate of 1 ml/min. The elute was monitored at 270 nm. The drug and internal standard were eluted separately at 5.40 and 2.27 min, respectively [Figure 2].

\subsection*{Characterization of beads by surface morphological analysis}
The prepared beads were subjected to Scanning Electron Microscopy (SEM), to study its shape and texture before and after release of the drug. The cross-section and pore size of the beads were also determined after an \textit{in-vitro} dissolution study of the beads. SEM analysis was carried out using the Jeol JSM-5300 Scanning Electron Microscope [Figure 1].

\subsection*{Entrapment efficiency}
Accurately weighed quantities of approximately 20 mg of beads were placed in 25 ml of Phosphate buffer pH 7.4. The solution was centrifuged using the centrifuge at 4200 RPM for 30 minutes; the supernatant layer of the liquid was assayed by UV-spectroscopy at 270 nm. The encapsulation efficiency was determined by the following equation:

\[
\text{Encapsulation Efficiency} = \frac{\% \text{ Drug content of formulation} \times \text{Amount of drug loaded}}{\text{Total weight of the dried Beads} - \text{Drug loss in the gelation media}}
\]

\subsection*{Swelling studies}
Swelling studies for beads was performed in dissolution media (Phosphate buffer pH 7.4.). The swelling index was calculated using the formula: Swelling index = \(\frac{(W_s - W_o)}{W_o \times 100}\), where \(W_s\) was the initial weight of beads and \(W_o\) was the weight of beads in the swelling medium.

\subsection*{Drug content determination by the HPLC method}
A Shimadzu HPLC system, equipped with a solvent delivery system model LC 10A, a UV-visible spectrophotometric detector model (SPD10AV) and a data processor model (-10R4A), was used. A Neuclosil C-18 column (250 x 4 mm I.D) 5 mm particle size (supplied by Machez-nasel Duven, Germany) was used. The mobile phase consisting of Acetonitrile : 0.02 M phosphate buffer 50 : 50 (v/v) (pH adjusted to 4.0 with o-phosphoric acid) was used for elution.

\subsection*{In-vitro drug release studies}
\textit{In-vitro} release studies for the formulated mosapride beads were performed using USP Type II apparatus at 75 RPM. The media was 900 ml of 0.1N HCl, which was maintained at 37 ± 0.5°C. Beads containing 20 mg of the drug were accurately weighed and placed into the dissolution apparatus. Samples were withdrawn at various time intervals, that

\begin{table}[h]
\centering
\caption{Formulation of mosapride alginate beads}
\begin{tabular}{|c|c|c|c|}
\hline
Batches & Drug (%) & Polymer (%) & Polymer : Gas forming agent(%) \\
\hline
Formulation-1 & 8 & 4 & 1 : 0.25 \\
Formulation-2 & 8 & 4 & 1 : 0.5 \\
Formulation-3 & 8 & 3 & 1 : 0.25 \\
Formulation-4 & 8 & 3 & 1 : 0.5 \\
\hline
\end{tabular}
\end{table}
is, 1, 2, 4, 6, 8, 10, 12, and 14 hours. The media was fully replaced during each sampling interval, because there could be chances of degradation of the drug. The samples were measured spectrophotometrically at 270 nm using a UV-spectrophotometer.

Stability studies
The formulated beads in formulations 1 and 3 were sealed in vials and kept for 90 days at 40°C/75% RH. After 90 days of exposure the beads were studied for drug content determination and in-vitro release.

Floating properties
Fifty beads were placed in 500 ml of 0.1 N HCl media. The
Floating properties of beads were evaluated in a dissolution vessel [USP Type II dissolution tester]. Paddle rotation speeds of 0 and 100 revolutions per minute were tested. Temperature was maintained at 37°±0.5°C. The percentage of floating samples was measured by visual observation.

RESULTS AND DISCUSSIONS

Four different formulations of mosapride-loaded alginate beads were formulated by using sodium alginate and hydroxypropyl methylcellulose. The formulated beads were spherical in shape and had a uniform texture. The SEM figures clearly depict that pores were absent on the surface of the formulated beads. The pore size of all the formulated beads, after in-vitro drug release, was found to be 90 to 100 µm by Scanning Electron Microscopy. The mean entrapment efficiency and drug content was studied in triplicate and the results were found to be satisfactory [Table 2].

Each value represents mean ± SD of three determinations.

Sodium alginate was used as a gelling polymer and along with it HPMC was used as a release retardant and rate controlling polymer. The combination of these two polymers was utilized for controlling the floating and release properties of mosapride from the beads, over a desired duration of time. The percentage drug release at the end of 14 hours from formulations 1, 2, 3, and 4 were found to be 90±0.2, 99.5±0.12, 94.9±0.15, and 98±0.13, respectively. The release profiles of the drug are shown in [Figure 3].

The swelling studies for beads were performed in a dissolution medium. The swelling studies that were carried out showed that maximum swelling for all batches took place 12 hours from exposure. The swelling of calcium alginate beads in the phosphate buffer was related to the Ca³⁺ and Na⁺ exchange. In the initial phase the Na⁺ ions present in the phosphate buffer exchanged with the Ca³⁺ ions bound to the COO⁻ groups of the mannuronic blocks. As a result, an electrostatic repulsion between the negatively charged COO⁻ groups increased, resulting in gel swelling. The exchanged Ca³⁺ ions precipitated in the form of insoluble calcium phosphate, which was reflected in the slight turbidity of the swelling medium. In the later phase of swelling, diffusion of Ca³⁺ from the polyguluronate blocks caused loosening of the tight egg-box structure, and thus permitted the penetration of additional amounts of media into the beads. From the above-mentioned formula for swelling studies, it was found that maximum swelling for all the formulations took place in the range of 25 to 33% of the initial weight of the beads.

The formulated beads in formulations 1 and 3 were sealed in vials and kept for 90 days at 40°C / 75% RH. The percentage drug release from formulations 1 and 3 after 90 days of exposure were found to be 90.05±0.20 and 95.8±0.15, respectively. The Floating properties of beads were evaluated in a dissolution vessel. One hundred percent floating was observed in all the formulated mosapride beads (formulations 1, 2, 3, and 4) with the simulated gastric fluid, pH 1.2, for 24 hours.

CONCLUSION

In the present study floating mosapride alginate beads were formulated by the ionotropic gelation method. The physical characterization, entrapment efficiency, drug content, and release profile were determined for the formulated mosapride beads. The formulated beads were found to be spherical in shape and had uniform texture, with a predetermined and controlled rate of release. Thus, the present results confirmed that the formulated mosapride beads were found to be stable, and the floating ability of the formulated beads was found to be excellent.

REFERENCES


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