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Ionotropically emulsion gelled polysaccharides beads: Preparation, *in vitro* and *in vivo* evaluation

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ABSTRACT

Floating famotidine loaded mineral oil-entrapped emulsion gel (MOEG) beads were prepared by the emulsion–gelation method. Different polysaccharides (sodium alginate and pectin), oil concentrations (10%, 20% and 30% w/w) and drug:polymer (D:P) ratios (1:1, 2:1 and 3:1) were used and their influence on beads uniformity, drug entrapment efficiency (DEE) and *in vitro* drug release, was studied. The results clearly indicated that retardation of drug release for 4 h was achieved by the oil hydrophobic diffusional barrier, especially in the presence of the compact network of alginate beads. Calcium alginate beads containing 20% oil and 2:1 D:P ratio, showed an optimum DEE of 88.32%. When evaluated *in vivo*, this formula displayed superior antiulcer activity (>2) over drug suspension or marketed conventional tablets.

1. Introduction

Gastroretentive systems could lengthen the gastric residence time of a dosage form for a period of time over which the drugs may be released gradually. These systems may delay the arrival of some drugs to their absorption site but are beneficial as carriers for drugs that act locally in the stomach (Murata, Sasaki, Miyamoto, & Kawashima, 2000), drugs that are poorly soluble at an alkaline pH (Machida, Inouye, & Tokumura, 1989) and drugs with a narrow window of absorption (Chungi, Dittert, & Smith, 1979). Among the various ways of increasing the retention time in the stomach, the low density systems are capable of floating on the gastric contents for a prolonged period of time allowing slow release of drugs at a desired rate (Singh & Kim, 2000). Numerous research efforts have been concentrated to develop multiple unit systems such as floating gel beads which showed superiority over single ones in terms of uniform distribution along the gastrointestinal tract, reduction of the intersubject variability in absorption and lowering the probability of dose-dumping characteristics (Rouge, Leroux, Cole, Doelker, & Buri, 1997). The tendency of multiple unit gel beads to possess floating nature as a result of oil incorporation was recently reported in the literature (Sriamornsak, Thirawong, & Puttipipatkhachorn, 2004; Choudhury & Kar, 2005).

As a dispersed phase, oil generates uniform emulsion creating multiple tiny chambers in the bead matrix for better buoyancy. The formed emulsion is stabilized by the surface active ability of alginate and pectin (Choudhury & Kar, 2005; Leroux, Langendorff, Schick, Vaishnav, & Mazoyer, 2003). The inclusion of oil provides a diffusional barrier towards drug escape from porous beads. In addition, the hydrophobic nature of oil reduces drug loss during entrapment processes. Because of their high volatility and porosity, volatile oils have major drawbacks of uneven sphere production, great loss of original size of beads and very rapid drug release. Furthermore, as compared to fixed oils, mineral oil has a relative lower density that reduces the amount required to give buoyancy (Sriamornsak et al., 2004), added to a more prolonged drug release characteristics (Choudhury & Kar, 2005).

In this regard, the present work deals with the formulation, *in vitro* characterization and *in vivo* evaluation of mineral oil-entrapped emulsion gel (MOEG) beads as a delivery system of famotidine. Famotidine, an H_2 receptor antagonist, suffers from incomplete and variable oral absorption (Hui, Kolars, Hu, & Fleisher, 1994) which occurs mainly in the proximal small intestine (Mehta, Doshi, & Joshi, 2003). Gastroretentive controlled release gel beads could continually supply famotidine in solution form to its most efficient site of absorption, where its bioavailability would be improved. Furthermore, local delivery of famotidine might increase the stomach wall receptor site availability, increasing its efficacy in reduction of acid secretion (Coffin & Parr, inventors, 1995). Moreover, an additional valuable advantage could be achieved after filling such beads in capsules, for providing light stability to this light sensitive drug.

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2. Materials and methods

2.1. Materials

Famotidine and sodium alginate were kindly supplied by Memphis Co. (Cairo, Egypt). Low methoxy (LM) pectin LM104 was obtained as gift sample from CP Kelco Co. (Denmark). Light mineral oil and anhydrous calcium chloride ($CaCl_2$) were obtained from El Nasr pharmaceutical chemicals (ADWIC) Co. (Cairo, Egypt). All other chemicals and reagents were of the highest purity available from local sources.

2.2. Methods

2.2.1. Preparation of famotidine loaded calcium alginate and calcium pectinate MOEG beads

Famotidine loaded MOEG beads were prepared by the emulsion–gelation method (Sriamornsak et al., 2004). In this method, a pre-gelation liquid of either 50 ml of 1% w/w sodium alginate solution or 25 ml of 2.5% w/w pectin solution was prepared. Mineral oil, in concentrations (10%, 20% and 30% w/w), was then added to the polymer solution to make 100-g mixtures. To ensure emulsion stabilization, the mixtures were homogenized at 10,000 rpm using a homogenizer (Erweka, type 4R401, Germany) for 10 min. Famotidine was then dispersed in the formed emulsion in different drug:polymer (D:P) ratios (1:1, 2:1 and 3:1 w/w). The bubble-free emulsion was extruded, using a 16G syringe needle into 250 ml gently agitated 0.1 M $CaCl_2$ solution at room temperature. The emulsion gel beads were allowed to stand in the solution for 20 min before being separated and washed with 3× 100 ml distilled water. The beads were air-dried at room temperature. The composition of different calcium alginate (A1–A9) and calcium pectinate (P1–P9) MOEG beads is shown in Table 1.

2.2.2. Characterization of MOEG beads

2.2.2.1. Study of the homogeneity and uniformity of beads. In order to prepare uniform beads (i.e. of the same size and density) it is essential that synthesis conditions such as viscosity, rate of falling of drops, stirring rate and distance between syringe and gelation medium, be maintained constant during the course of the formation of beads. Variation in any of these parameters during the bead formation process may result in the production of non-homogenous and non-uniform beads, affecting the overall results to an appreciable extent (Bajpai & Tankhiwale, 2008). Also, process homogeneity was greatly influenced by emulsion homogenization which yields fine dispersion of oil and water with size uniformity. Without homogenization, the oil might separate out from the solution and uneven sized beads were formed (Choudhury & Kar, 2005). In order to test the product uniformity, the individual diameters of 20 dried MOEG beads were measured with a calliper (Cole-Parmer instrument Co.) as reported (Murata et al., 2000). The results are expressed as the mean diameter (mm) ± standard deviation. The sphericity of the beads was also determined by axial and diametral measurements.

2.2.2.2. Density measurements. The mean weight and diameter of the beads were measured and used to mathematically calculate the densities of the spherical calcium alginate and pectinate beads using the following equations:

$$D = \frac{M}{V} \quad (1)$$

$$V = \frac{4}{3}\pi r^3 \quad \text{(for a typical sphere)} \quad (2)$$

where D is the density of the beads; M is the weight of the beads; V is the volume of the beads; r is the radius of the beads.

2.2.2.3. Determination of the beads buoyancy and integrity. The MOEG beads ($n = 20$) were soaked in beakers filled with 50 ml of 0.1 N HCl (pH 1.2). The floating ability of the beads was measured by visual observation for an overall duration of 6 h. The preparation was considered to have buoyancy in the test solution only when all of the beads floated (Cooreman, Krausgrill, & Hengels, 1993). The integrity of the beads was also observed visually during the buoyancy test.

2.2.2.4. Determination of drug entrapment efficiency (DEE). An accurately weighed amount of 50 mg of famotidine loaded MOEG beads was dissolved in 250 ml (in case of alginate beads) or 500 ml (in case of pectinate beads) of phosphate buffer pH 7.4 by stirring for 6 h using magnetic stirrer. The resulting solution was then filtered using 0.45 μm Millipore filter (Sartorius, GmbH, Germany). Famotidine content was determined spectrophotometrically (Shimadzu UV–visible 1601 PC, Kyoto, Japan) at the predetermined λ_{max} (286 nm). The determinations were made in triplicate and DEE was calculated according to the following equation:

$$\text{DEE}(\%) = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100 \quad (3)$$

2.2.2.5. Scanning electron microscopy (SEM). Morphological examination of the surface and internal structure of the dried MOEG beads was carried out using a scanning electron microscope (JEOL JEM-1200 EX II, Japan) equipped with secondary electron detector at an accelerating voltage of 10 kV. The samples were coated with gold to a thickness of about 30 nm in a vacuum evaporator. The internal structure of beads was examined by cutting them with a steel blade.

2.2.3. In vitro famotidine release studies

The *in vitro* release studies were carried out using USP rotating basket apparatus-Pharma test, type PTW-2, Germany (apparatus I). Amounts of beads equivalent to 40 mg famotidine were introduced into the baskets which were rotated at 50 rpm in 900 ml 0.1 N HCl (pH 1.2), maintained at 37 ± 0.5 °C. Aliquots of 5 ml of the solution were withdrawn at predetermined time intervals and replaced by fresh dissolution medium. The withdrawn samples were analyzed for famotidine content spectrophotometrically at λ_{max} (265 nm). The release of famotidine plain powder and marketed conventional famotidine tablet were studied as well. None of the ingredients used in the bead formulations interfered with the assay. The results were expressed the mean of three experiments.

2.2.3.1. Analysis of the in vitro release studies. Mathematically, the release profiles of the various formulae in 0.1 N HCl were compared using the similarity factor (f_2) defined in FDA Scale-up and Post-Approval Change (SUPAC) guidelines for solid dosage forms (US Department of Health and Human Sciences, 1997) using the following equation:

$$f_2 = 50\log\{[1 + 1/n\sum(R_t - T_t)^2]^{-0.5} \times 100\} \quad (4)$$

where n is the number of time points and R_t and T_t are the percent drug released at each time point for the reference and the test. For comparison between each set of two formulae, the formula containing the lower D:P ratio and the lower oil concentration were taken as references to elucidate the effect of oil concentration and D:P on the *in vitro* drug release. Also, the marketed conventional tablet was considered as a reference for comparative pur-