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Physical characterizations and sustained release profiling of gastroretentive drug delivery systems with improved floating and swelling capabilities

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ABSTRACT

The aim was to develop gastroretentive drug delivery systems (GRDDSs) by combining floating and swelling. GRDDS tablets formulated with hydroxyethylcellulose (HEC), chitosan (CS) and sodium bicarbonate (SB) for evaluating floating capacity (floating lag time and duration) and swelling characteristics. CS was used because it was swellable in acidic media and biocompatible. Losartan was incorporated into the optimized formulations for sustained release profiling. Results demonstrated that for those formulations at HEC:CS ratio of 5:5 containing CS, both the floating lag time and floating duration were optimal and reached the preferred swelling effect and sustain for 24 h. Adding SB improved the floating capabilities for all ratios of HEC:CS, but reduced the swelling ability for those formulations containing a higher portion of low viscosity grade CS. Sustained release profiles for losartan in those formulations were achievable, using all viscosity grades of CS at all examined HEC:CS ratios; however, it is more adjustable at different HEC:CS ratios when using a lower viscosity grade of CS. Optimized GRDDS formulations for losartan composed of an equivalent ratio of HEC to CS with 20 mg SB resulted in the tablets floating for more than 16 h and an adjustable sustained release profile.

1. Introduction

Despite considerable advancements in drug delivery, the oral route remains the preferred route because of the low cost of therapy and ease of administration, leading to high levels of patient compliance. Oral controlled-release drug delivery systems provide drug release at a predetermined, predictable, and controlled rate, and have drawn considerable attention. However, some drugs have demonstrated poor bioavailability because of incomplete absorption or degradation in the gastrointestinal tract (GIT) (Hoffman, 1998; Nayak et al., 2010; Streubel et al., 2006). Therefore, a gastroretentive drug delivery system (GRDDS) is developed, because prolonging the gastric retention is sometimes desirable for drugs that: (i) are locally active in the stomach; (ii) have a narrow absorption window in GIT; (iii) are unstable in the intestinal or colonic environment; or (iv) exhibit low solubility at high pH regions (Kagan et al., 2006; Murphy et al., 2009). GRDDS can improve the bioavailability of drugs that exhibit site-specific absorption (Chawla et al., 2003).

GRDDS can be approached by: (i) a low density dosage form (DF) that causes buoyancy above gastric fluid; (ii) a high density DF that sinks in the bottom of the stomach; (iii) a bioadhesion to the stomach mucosa; or (iv) a limited emptying of the DF through the pyloric sphincter by swelling or unfolding to a larger size (Chawla et al., 2003; Hoffman et al., 2004; Klausner et al., 2003; Singh and Kim, 2000). Moreover, various combined gastroretentive mechanisms were also developed to enhance gastroretention capabilities. The floatability of captopril caused by hydroxypropyl methyl cellulose (HPMC) matrices depends on the porosity, and an insufficient porosity can be increased by generating carbon dioxide (CO_2) bubbles obtained from the reaction of sodium bicarbonate (SB) with an acidic dissolution medium (Jimenezmartinez et al., 2008). Similarly, a previous study formulated metformin hydrochloride, which is more effectively absorbed in the upper intestine, as a floating matrix tablet using a gas generating agent (SB and citric acid) and a gel forming hydrophilic polymer (HPMC) with a hardness level between 6.8 and 7.5 kg/cm^2, demonstrating a floating time of more than 8 h and promising drug release results (Basak et al., 2007). Strübing et al. chose Kollicoat® SR as an excipient for direct compression, leading to high tablet hardness at low compression forces. Nevertheless, the density of the tablet core was relatively low, demonstrating that Kollicoat® SR and SB were able to ensure a low initial density of the floating system and overcompensate for the sinking characteristics of the model drug, propranolol HCl (Strübing et al., 2008a, 2008b). A novel sustained GRDDS of

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ofloxacin was developed using SB (floating), crospovidone and betacyclodextrin (swellable), and psyllium husk and HPMC (bioadhesive) (Chavanpatil et al., 2006). Ciprofloxacin is mainly absorbed in the proximal areas of the gastrointestinal tract, and Varshosaz et al. produced floating-bioadhesive tablets to lengthen the stay of ciprofloxacin in its absorption area, and effervescent tablets were designed using sodium carboxymethyl cellulose, HPMC, polyacrylic acid, polymetacrylic acid, citric acid, and SB (Varshosaz et al., 2006). Additionally, the blends of ciprofloxacin, HPMC, swelling agents (crospovidone, sodium starch glycolate, and croscarmellose sodium), and SB were found to show more favorable swelling, drug release, and floating characteristics than those of marketed-product (CIFRAN OD®) (Arza et al., 2009). We previously reported a swelling/floating gastroretentive drug delivery system based on a combination of hydroxyethyl cellulose and sodium carboxymethyl cellulose for losartan (Chen et al., 2010). Although previous studies have attempted to develop a dosage form with a longer gastrointestinal transit time, floating and swelling delivery systems seem to offer greater safety for clinical uses than do other approaches (Li et al., 2003).

Chitosan (CS) is a cationic polysaccharide, which differ in their degree of *N*-deacetylation (40–98%) and molecular weight (50,000–2,000,000 Da), and increasing the degree of deacetylation increases the viscosity. These two characteristics are very important to the physico-chemical properties of CS and play an important role in drug delivery system. CS is a weak base with a pK_a value about 6.2–7.0 and; therefore, is insoluble at neutral and alkaline pH values. In acidic medium, the amine groups of the polymer are protonated resulting in a soluble, positively charged polysaccharide (Hejazi and Amiji, 2003). Because of its characteristics of swellable hydrogel polymer in acidic media, as well as being biocompatible, biodegradable, and nontoxic, CS draws considerable attention for medical and pharmaceutical applications (Chang and Lin, 2000). Hydroxyethyl cellulose (HEC) is a nonionic, water-soluble polymer widely used in pharmaceutical formulations (Chen et al., 2010). Losartan is an angiotensin-receptor antagonist used as an antihypertension medicine. Following oral administration, losartan is rapidly absorbed and approximately 14% of a losartan dosage is then metabolized into active carboxylic acid metabolite (E3174); but E3174 is 10- to 40-fold more potent than its parent compound, and the estimated terminal half-life ranges from 6 to 9 h (Sica et al., 2005). The low bioavailability of losartan may be due to a combination of incomplete absorption and a variable first-pass metabolism (Sica et al., 2005). Therefore, the aim of this study was to report the development of a swellable and floatable GRDDS, based on the combination of CS, HEC and SB to shorten the floating lag time and prolong the floating duration with a sustained drug release pattern.

2. Materials and methods

2.1. Materials

Hydroxyethyl cellulose 250HHX (HEC, viscosity 3400–5000 cp, estimated MW = 1600 kDa) was supplied by Ashland Inc. (Covington, Kentucky, USA). Chitosan (CS) with a viscosity of 200–800 cp (AMmw CS, 75–85% degree of deacetylation, MW = 190–310 kDa) and 800–2000 cp (AHmw CS, 75–85% deacetylation, MW = 310–375 kDa) were obtained from Aldrich (Germany), whereas CS with a viscosity < 200 cp (FLvis CS, M_w = 108,300, M_n = 41,970), 200–400 cp (FMvis CS, M_w = 260,700, M_n = 172,200), and >400 cp (FHvis CS, M_w = 378,200, M_n = 207,400) were supplied by Fluka (Switzerland). Losartan potassium was provided by Ipca Laboratories Limited (Tamil Nadu, India), and the SB was obtained from Riedel-de Haën (Germany). All other chemicals used were reagent or pharmaceutical grade.

2.2. Characterization of swelling and floating of GRDDS

2.2.1. Fabrication of GRDDS tablets

The HEC, CS with various viscosities, and SB were blended to formulate tablets at different compression pressures (0.25, 0.5, and 1 ton) to elevate the floating capacity. Physical characterizations of the tablets included: swelling ratio based on diameter variation, floating lag time, and floating duration to establish a comprehensive understanding of the floating and swelling properties of various formulations. Then, 50 mg of the model drug, losartan, incorporated into the optimal formulations, was prepared using the direct compression method for *in vitro* characterization. The mixture was compressed on a Carver Laboratory Press tableting machine, using flat-faced punches (diameter 12 mm) for 6 s.

2.2.2. Floating capacities

The floating capacities were examined by following the procedure reported by Baumgartner et al. (2000). Briefly, the time that the tablets required to reach the water surface (floating lag time) and the period that the tablets constantly float on the water surface (designated as floating duration) were evaluated in a dissolution vessel (Vankel, VK7020, Varian Inc.) filled with 900 mL of either deionized water (DIW) or simulated gastric fluid (SGF) without pepsin (pH 1.2) at a temperature of 37 ± 0.5 °C with no stirring. Triple measurements were performed for each examined formulation (n = 3).

2.2.3. Determination of swelling ratio

The swelling of tablet is three dimensional and the extent of swelling can be measured either by the % weight gain of swollen tablet or by the % volume increment calculated by $\pi \times (\text{diameter}/2)^2 \times$ thickness with the assumption that the tablet swelled as a cylindrical form. The % weight gain method has been reported previously (Chen et al., 2010). However, it was thought that the diameter of swollen tablet would be the determining factor that if swollen tablet could be retained by the opening of pylorus. Therefore, tablets with a diameter of 12 mm were produced and % of diameter increment was measured as an indicator of the extent of swelling to ensure the ability of gastro-retention. The swelling studies were conducted using Vankel dissolution apparatus. No rotation speeds were applied. The tablets were immersed in 900 mL of either DIW or SGF at 37.0 ± 0.5 °C. At predetermined intervals (0.5, 1, 2, 4, 6, 8, 12, 16, and 24 h), the swollen tablets were removed from the solution, immediately wiped with a paper towel to remove surface droplets, and measured to ascertain the diameters. The swelling ratio (S_r) was calculated according to the following equation:

$$\text{Swelling ratio} = \frac{S_t - S_i}{S_i} \quad (1)$$

where S_i and S_t represent the initial diameter of the dry tablet and that of the swollen tablet at time t, respectively. The data represent mean ± SD from at least three samples per formulation.

2.3. Release studies

Drug release from GRDDS tablets was performed in 900 mL of either DIW or SGF at 37 ± 0.5 °C at 50 rpm, based on the apparatus II method (USP XXIX) (VK7020, Vankel, UK) over 24 h. The medium (5 mL) was sampled at predetermined times (0, 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 20, and 24 h) and replaced with a fresh medium of the same volume. The drug concentration was measured using an ultraviolet/visible spectrophotometer (V-550, Jasco, Japan) at a wavelength of 254 nm using a 1.0-cm quartz cell that had been validated to have acceptable precision and accuracy for intra- and inter-day assays. The average percentage of the drug dissolved at each sampling time was calculated after correcting for the cumulative amount removed

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