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Controlled-release of antacids from biopolymer microgels under simulated gastric conditions: Impact of bead dimensions, pore size, and alginate/pectin ratio

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ABSTRACT

The highly acidic nature of the gastric fluids inside the human stomach can cause have health problems in certain individuals *e.g.*, acid reflux and ulcers. Antacid-loaded biopolymer microgels can be used to control the acidity of the gastric fluids, which may be useful for developing functional foods to treat these problems. In this study, the impact of biopolymer microgel dimensions and composition on the dissolution rate of encapsulated antacid was determined under simulated gastric conditions. The microgels were formed by injecting antacid (magnesium hydroxide) and biopolymers (alginate or alginate/pectin) into a calcium chloride solution to promote cross-linking. Microgels of varying dimensions were formed using either a hand-held syringe or a vibrating nozzle encapsulation device with different nozzle sizes. The rate of antacid dissolution was measured using an automatic titration device (pH stat) that added HCl solution into the simulated gastric fluids to maintain a constant pH of 2.5. The antacid dissolution rate decreased with increasing microgel diameter (300 to 1660 μm) and decreasing pore size (0.8 to 2.0% alginate). The slowest dissolution rate was observed in microgels containing 80% alginate and 20% pectin, which may have been due to the impact of biopolymer composition on bead dimensions and pore size. The results of this study may be useful for the design of biopolymer microgels that can control the release of antacids in the stomach, thereby leading to better control over the pH of the gastric fluids.

1. Introduction

Many individuals suffer from health problems related to the highly acidic nature of the gastric fluids within the human stomach, *e.g.*, those with gastroesophageal reflux disease, erosive esophagitis, and gastric ulcers (Leiman et al., 2017; Maton & Burton, 1999; Pettit, 2005). The pH of the stomach can be controlled by using antacids that dissolve in the gastric fluids and neutralize the stomach acids (Maton & Burton, 1999) or by using drugs that inhibit gastric proton pumps (Brett, 2005; DeVault & Talley, 2009; Pettit, 2005). However, these treatments can lead to an appreciable increase in the pH of the gastric fluids, thereby allowing potentially harmful bacteria to proliferate within the stomach, such as *Clostridium difficile* (Bardou & Fortinsky, 2015; Jimenez, Drees, Loveridge-Lenza, Eppes, & delRosario, 2015). Moreover, increasing the pH of the gastric environment can reduce gastric protease activity (Maton & Burton, 1999) and cause malabsorption of vitamins and minerals, such as vitamin B_{12}, iron, and calcium (DeVault & Talley, 2009). Consequently, there is interest in improving the available methods of controlling the pH of the gastric fluids in these individuals (Wang et al., 2013). This could be achieved by developing treatments that can control the pH of the gastric fluids over an extended period. One method that has been proposed to achieve this goal is to develop controlled-release antacids using encapsulation technologies (DeVault & Talley, 2009). The aim of the current study, was therefore to develop antacid-loaded biopolymer microgels that could prolong the dissolution of antacids within the stomach, and thereby allow better control of the pH of the gastric fluids.

Recently, we showed that magnesium hydroxide, $Mg(OH)_2$ could be encapsulated within alginate microgels (Zhang, Chen, Zhang, Deng, & McClements, 2016; Zhang, Zhang, & McClements, 2017). Magnesium

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hydroxide is insoluble at neutral pH, but slowly dissolves at acid pH. Consequently, it can partially neutralize stomach acids when it is dispersed in gastric fluids (Maton & Burton, 1999):

$$Mg(OH)_2 + 2HCl \longleftrightarrow MgCl_2 + 2H_2O \quad (1)$$

$$H^+ + OH^- \longleftrightarrow H_2O \quad (2)$$

The purpose of our previous studies was to develop biopolymer microgels that could encapsulate digestive enzymes (such as lactase and lipase) and protect them from the harsh acidic conditions in the human stomach, while maintaining their activity within the small intestine (Zhang et al., 2016; Zhang et al., 2017). The antacid was incorporated inside the microgels to maintain neutral pH conditions within their interior as they passed through the gastric fluids, thereby retaining the activity of the encapsulated enzymes. However, these systems may also be useful for controlling the pH of the stomach by altering the dissolution rate of the encapsulated magnesium hydroxide when exposed to gastric fluids. Consequently, the impact of microgel properties, such as dimensions, pore size, and composition, on their ability to control the dissolution of encapsulated magnesium hydroxide under simulated gastric conditions was determined. Many previous studies have shown that the properties of alginate microgels can be manipulated to alter their structural, physicochemical, and functional properties (Chaudhari, Kar, & Singhal, 2015; Gombotz & Wee, 2012; Jain & Bar-Shalom, 2014; Leong et al., 2016). For instance, this can be achieved by varying the alginate concentration (Li, Hu, Yumin, Xiao, & McClements, 2011; Puguan, Yu, & Kim, 2015; van Leusden et al., 2017), altering the cross-linker concentration (Li et al., 2011), mixing the alginate with another biopolymer (Bekhit, Sanchez-Gonzalez, Ben Messaoud, & Desobry, 2016; Belscak-Cvitanovic et al., 2015; Guo & Kaletunc, 2016), or changing the fabrication conditions (Gombotz & Wee, 2012; van Leusden et al., 2017). We therefore used some of these approaches to alter the properties of the biopolymer microgels used to encapsulate the antacid. Interestingly, alginate itself has been shown to be able to suppress acid reflux problems by increasing the viscosity of the gastric fluids, thereby preventing the acids reaching the esophagus (Rohof, Bennink, Smout, Thomas, & Boeckxstaens, 2013). Consequently, any alginate that leaks out of the biopolymer microgels used in this study may also inhibit acid reflux by this mechanism.

The results of the current study may lead to the development of biopolymer microgels that can be used to help treat individuals with health problems associated with gastric acidity, or that can be used to encapsulate and deliver acid-sensitive bioactive agents to the gastrointestinal tract (GIT). These microgels may be suitable for utilization within supplements or functional foods specifically designed for particular segments of the population.

It should be noted that other types of food-grade delivery systems may also be useful for antacid encapsulation and controlled release in the stomach. For instance, antacids could be encapsulated in protein microgels, liposomes, or multiple (W/O/W) emulsions. Each of these systems is likely to have its own advantages and disadvantages, and further studies on other types of delivery systems would certainly be interesting.

2. Materials and methods

2.1. Materials

Alginic acid (sodium salt), pectin, calcium chloride, and magnesium hydroxide were purchased from Sigma Chemical Company (St. Louis, MO). The manufacturers reported that the pectin was extracted from citrus peel and had a galacturonic acid content ≥74.0% (dried weight basis). Mucin from porcine stomach, porcine bile extract, sodium chloride, monobasic phosphate and dibasic phosphate were obtained from either Sigma-Aldrich (Sigma Chemical Co., St. Louis, MO) or Fisher Scientific (Pittsburgh, PA). All chemicals used were analytical grade. Double distilled water was used to prepare all solutions.

2.2. Preparation of antacid-loaded biopolymer microgels

Individual polysaccharide solutions (0.8 to 2.0%, w/w) were prepared by dissolving powdered pectin or alginate in phosphate buffer and continuously stirring at 50 °C for 4 h, then reducing the temperature to 35 °C with continuous stirring until they were fully dissolved. Mixed polysaccharide solutions were prepared by mixing different ratios of pectin solution (2.0%, w/w) and alginate solution (2.0%, w/w) together. The overall polysaccharide content in each of the mixed solutions was kept constant at 2.0% (w/w), but the percentage of pectin present was varied from 0 to 50% by varying the amount of the two solutions added. Encapsulated antacid systems were prepared by dispersing powdered $Mg(OH)_2$ (0.15%, w/w) into the polysaccharide solutions to obtain the final mixtures. After continuously stirring, biopolymer microgels were formed by injecting the final polysaccharide mixtures into 10% calcium chloride solution using either a commercial encapsulation instrument (Encapsulator B-390, BUCHI, Switzerland) with a 120, 150, or 300 μm vibrating nozzle or a simple hand-held syringe (BD Safety-Lok 10 mL Syringe with a 0.6 mm-diameter tip, Franklin Lakes, NJ). The encapsulation device was operated under fixed conditions: frequency 800 Hz; electrode 800 V; and pressure 500 mbar. The microgels formed were kept in the Ca^{2+} solution for 1-h at ambient temperature to promote cross-linking and bead hardening. The non-encapsulated antacid systems were prepared using a similar procedure, but the powdered $Mg(OH)_2$ was added to the microgel suspension after it had been formed.

2.3. In vitro digestion model

The microgels were passed through a simulated gastrointestinal tract (GIT) that included mouth and stomach phases. The GIT model used was a simplification of an earlier model that we have used to study the potential gastrointestinal fate of microgels (Zhang et al., 2016; Zhang et al., 2017).

2.3.1. Initial system

7.5 g of the initial microgel systems were placed into a glass beaker that was transferred into an incubator shaker and then swirled at a rotation speed of 100 rpm for 15 min at 37 °C.

2.3.2. Mouth phase

7.5 g of simulated saliva fluid containing 0.03 g/mL mucin was preheated to 37 °C and then adjusted to pH 6.8. After being mixed with the initial systems, the mixture was swirled in the incubator shaker for 2 min at 37 °C to mimic oral conditions.

2.3.3. Stomach phase

15 g of simulated gastric fluid was preheated to 37 °C, and then the pH was adjusted to 2.1. After being mixed with 15 g of the sample resulting from the mouth phase, the pH of the mixture was initially around 2.5. The samples were then placed within the incubator shaker and swirled for 2 h at 37 °C to mimic gastric conditions. In some experiments, the change in the pH of the gastric fluids during incubation under simulated stomach conditions was measured over time. In other experiments, the pH of the simulated gastric fluids was kept constant at pH 2.5 by adding HCl solution into the system using an automatic titration unit (Metrohm, USA Inc.)

2.4. Determination of particle dimensions

The particle size distribution and mean particle diameter of the microgels was measured using laser diffraction (Mastersizer 2000, Malvern Instruments Ltd., Malvern, Worcestershire, UK) (McClements & McClements, 2016). Samples were diluted in aqueous buffer solutions