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Dissolution kinetics of pH responsive alginate-pectin hydrogel particles

Jingxin Guo, Gönül Kaletunç *

Department of Food, Agricultural, and Biological Engineering, Ohio State University, Columbus, OH, United States

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ABSTRACT

Encapsulation is used for protection of bioactive compounds during processing, storage, and passage through the upper gastrointestinal (GI) tract and delivery to the small intestine. A number of pH responsive synthetic polymers are approved for drug delivery but are not allowed for food applications. We developed a biopolymer mixture composed of alginate and pectin that can form hydrogel when the pH is below 3.0. We also produced novel disc shaped particles which can potentially enhance the particle adhesion in intestines. As the pH increases, Al-P hydrogels go through a gel-sol transition and the dissolution kinetics of the hydrogel dominates the bioactive compound release. The goals of this study are to investigate the relative effects of factors contributing to the dissolution kinetics of Al-P hydrogel and to develop mathematical models characterizing the degradation behavior of the hydrogels under product storage and lower GI tract conditions. The volume change of spherical and disc shaped particles at pH 3.0 showed that the hydrogel particles would be stable in low pH beverages during storage. At pH 5.0 and 7.0, hydrogel particle dissolution followed a zero-order kinetic model. The 2.8% TGC 43:57 wt% Al-P disc particles had the fastest and the 2.2% TGC 82:18 wt% Al-P spherical particles had the slowest volume dissolution rate at pH 7.0 and 37 °C. Activation energies of hydrogel particles were significantly affected by pH, particle shape and Al to P ratio. Such a biopolymer system which responds to pH provides an opportunity to use food as a vehicle for targeted delivery of bioactive compounds.

1. Introduction

Hydrogels have been investigated for delivery of nutrients and drugs in food and pharmaceutical industries and building scaffolds and sensors in medical applications. A variety of synthetic and natural polymers of hydrophilic properties were used as encapsulant to form hydrogels (Peppas, Hilt, Khademhosseini, & Langer, 2006). In food applications, FDA requires that encapsulant materials should have the "Generally Regarded As Safe (GRAS)" status. Typically, encapsulation occurs by physical entrapment of bioactive materials within the polymer networks of hydrogel, thereby inhibiting interactions between encapsulated material and external environment (Kuang, Oliveira, & Crean, 2010). Then, hydrogel particles of biopolymer origin, containing bioactive materials can be incorporated in the food material for delivery of beneficial compounds to the human body. Encapsulant provides a protection to the bioactive molecules by isolating them from external environment encountered during food processing, storage, and human stomach (Anal & Singh, 2007; Cabane, Zhang, Langowska, Palivan, & Meier, 2012; Drusch, 2007). It is also expected that upon reaching intestines, hydrogels should swell or dissolve so that beneficial compounds can be released in human body. Such "smart polymer" systems which are sensitive to physical and chemical stimulants were developed for controlled delivery of nutrients and drugs.

A number of protein and polysaccharides were used alone or in combination to form hydrogels (Wang, Bamdad, Song, & Chen, 2012). Numerous natural polysaccharides including agar, alginate, carrageenan, pectin, gelatin can form hydrogels under different conditions, and are considered as GRAS (FDA, 2015). Their biocompatibility and biodegradability are advantageous as delivery media applied in the food industry. The hydrogels formed by these materials have been produced (Burey, Bhandari, Howes, & Gidley, 2008; Ré, Santana, & d'Avila, 2009) by different encapsulation techniques. Droplet extrusion is a fabrication method where in a biopolymer solution is extruded through an opening into a curing solution. The morphology and dimension of the resultant Ca-alginate particles were shown to depend on the flow rate of the feed solution, the diameter of the opening, surface tension and the viscosity of the polymer solution (Burey et al., 2008; Chan, Lee, Ravindra, & Poncelet, 2009). The typical dimension of the hydrogel particles fabricated by this technique is 0.5–6 mm with or without combining other techniques (Burey et al., 2008). Smaller hydrogel particles were reported to be generated with the droplet extrusion method combined with other techniques, such as electrostatic dripping, laminar jet breakup, jet cutting, jet nebulizer and disc nebulizer (Ré et al., 2009).

Sodium alginate and pectin are anionic polysaccharides which form biodegradable hydrogels (Wang et al., 2012). Alginate comprises both guluronic acid (G) and mannuronic acid (M), and pectin only galacturonic acid. The abundant carboxylate and hydroxyl groups in both alginate and pectin result in a high hydrophilicity, which leads to polymer chain extension by the charge repulsion and to a high

* Corresponding author at: 590 Woody Hayes Dr., Columbus, OH 43210, United States.
E-mail address: kaletunc.1@osu.edu (G. Kaletunç).

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absorption of water (Oakenfull & Scott, 1984; Wang et al., 2012). The gelation of alginate or low methoxyl (LM) pectin requires the presence of divalent cations, while high methoxyl pectin (HM) requires sugar (Thom, Dea, Morris, & Powell, 1982; Walther, Hamberg, Walkenström, & Hermansson, 2004); however synergistic gelation of alginate-pectin mixtures occurs at low pH reported between pH 3.3 and 4 by various researchers depending on alginate-pectin ratio and G/M of alginate and degree of esterification (DE) of pectin (Higuita-Castro et al., 2012; Morris & Chilvers, 1984; Rao & Cooley, 1995; Thom et al., 1982; Toft, 1982; Toft, Grasdalen, & Smidsrod, 1986; Walkenström, Kidman, Hermansson, Rasmussen, & Hoegh, 2003). Morris and Chilvers (1984) reported that alginate or pectin did not gel under the same conditions that alginate-pectin blend formed a gel. Alginate-pectin mixtures have been used to encapsulate vitamin C, anthocyanins (Higuita-Castro et al., 2012) and folic acid (Madziva, Kailasapathy, & Phillips, 2005). Madziva et al. (2005) used an alginate and pectin gel mixture dropping into 0.1 to 1.0 M of calcium chloride to fabricate hydrogel particles. Higuita-Castro et al. (2012) showed that alginate-pectin hydrogel particles were formed while pH dropped from 6.0 to 3.0 by adding Gluconoδ-lactone to biopolymer solution. However, the controlled dissolution of hydrogels is very important for release of incorporated bioactive compounds.

Dissolution of ionic alginate hydrogels was shown to be controlled by the biopolymer molecular weight, composition or the conditions of surrounding environment (Augst, Kong, & Mooney, 2006). Several studies exist in literature for dissolution behavior of alginate and pectin only gels (Bajpai & Sharma, 2004; Kikuchi et al., 1999; Lee & Mooney, 2012; Mater et al., 1995; Sriamornsak & Nunthanid, 1998; Xing et al., 2003; Thakur, Singh, Handa, & Rao, 1997; Lopez da Silva and Rao, 2006). Although, biopolymer blend hydrogels such as Al-P can provide more opportunities for applications of environmental stimuli responsive drug and nutrient delivery, the factors influencing their fabrication and dissolution characteristics have not been elucidated.

The pH responsive characteristic distinguishes Al-P hydrogel from alginate or pectin only hydrogels since neither of them alone form a pH responsive gel. As the pH increases, Al-P hydrogels are expected to go through a gel-sol transition and the kinetic of this transition can be a key factor in controlled release of bioactive compound. Several factors including temperature, alginate to pectin ratio, and the pH of the medium contribute to the dissolution of the hydrogel. The goals of the current study are to evaluate the effect of the encapsulation parameters; the alginate-pectin ratio, flow rate, dripping distance, and pH of curing solution on the morphology and mechanical properties of the hydrogel particles and to investigate the relative effects of the factors contributing to dissolution kinetics of Al-P hydrogel particles. The findings are used to develop mathematical models characterizing the dissolution behavior of the hydrogels at pH 5.0 and 7.0, the environment that can be associated with a full stomach and the small intestine and colon respectively (Guerra et al., 2012; Kong & Singh, 2008). The results of dissolution kinetics of hydrogels can be used for design of hydrogel based nutrient delivery systems.

2. Materials and methods

2.1. Materials

Alginate (SF 120) was obtained from FMC Biopolymer (Philadelphia, PA). Guluronic to mannuronic acid ratio (G/M) of alginate was 1.7. High methoxyl content pectin (Pretested® Pectin, rapid and slow-set) were provided by TIC Gum (White Marsh, MD). Rapid set pectin had a degree of esterification (DE) 71–75% and slow-set pectin had a DE of 63–67%. Reagents (hydrochloric acid, potassium chloride, citric acid, sodium citrate, sodium phosphate monobasic and sodium phosphate dibasic) to prepare buffer solutions of pH 1.2, 3.0, 5.0 and 7.0 were purchased from Fisher Scientific (Waltham, MA).

2.2. Preparation of gel solutions

Each of 2% (wt) alginate (Al) and 4% (wt) slow and 4% (wt) rapid pectin (P) solutions was prepared by dispersing the powders in deionized water with a high shear mixer for 30 min at ambient temperature. After incubating at 4 °C for 8 h to allow bubbles to rise, the individual solutions were mixed in various ratios to obtain the desired total gum concentration (TGC) and Al to P ratios. The mixtures then were stored at 4 °C for an additional 12 h for bubbles to rise. For screening experiments, Al-P mixtures of 2.2–3.0% (wt) TGC and Al-P weight percent ratios of 33:67, 43:57, 67:33, and 82:18 were prepared. Pectin amount in the mixture was equally divided between slow and rapid set pectin.

2.3. Hydrogel particle preparation

The Al-P solutions were extruded through a 0.337 mm diameter (23 G) needle (Hamilton, Nevada) with a peristaltic pump (Cole Parmer, IL) at volumetric flow rates of 0.017 or 0.022 ml/s. The droplets extruded through the needle formed hydrogel particles when they came into contact with gently agitated low pH buffered solution. 0.1 M pH 1.2 HCl/KCl buffer or pH 3.0 citric acid/sodium citrate buffer were prepared as curing medium for hydrogel particles. For screening experiments, the curing buffers of pH 1.2 or 3.0, dropping distances of 1.5–20 cm, Al-P solution flow rates of 0.017 or 0.022 ml/s, TGC of 2.2–3.0 wt% and Al to P ratios stated in Section 2.2 were used to evaluate their effects on particle size and shape. Al-P hydrogel particles were cured at 4 °C for 2 h prior to characterization of the dimensions and shape. Based on focusing the study on regular shaped particles and relatively higher gel strength, the conditions at Al to P ratio of 82:18 wt% Al-P at 2.2 wt% TGC and 43:57 wt% Al-P at 2.8 wt% TGC in pH 1.2 curing buffer were selected for further studies. Throughout the text, 82:18 wt% Al-P mixture at 2.2 wt% TGC is referred as formulation 1 (F1) and 43:57 wt% Al-P mixture at 2.8 wt% TGC is referred as formulation 2 (F2).

2.4. Particle size and shape characterization

A digital microscope (Amoeba Dual Purpose Digital Microscope, Celestron, CA) was used to photograph hydrogel particles placed on a microscope slide at 10× magnification. Top and side view images of the hydrogel particles were obtained. The particle dimensions were determined using Image J software (National Institutes of Health, Bethesda, MD).

2.5. Gel mechanical properties

2.5.1. Sample preparation

Hydrogel cylinders under four combinations of 43:57 and 82:18% (wt) Al to P ratio and 2.2 and 2.8% (wt) TGC were prepared to measure gel strength and elasticity. The gel solutions were mixed and poured into a plexiglass tube of 1 cm internal diameter and 1 cm height. One end of the tube was sealed with parafilm, and the tube was filled with the mixture from the open side. The tube was placed vertically inside a beaker filled with 40 ml of pH 1.2 buffer solution to promote gel formation. After 1.5 h, an adequately thick gel layer formed on the open side. Then the parafilm was removed and the tube was inverted to expose the other end to the curing solution for 1.5 h. The tube was placed horizontally in the curing solution to allow the buffer solution to diffuse into the gel from both ends. After 2 h, the gels were ready for mechanical property tests.

2.5.2. Gel mechanical properties measurement

Mechanical properties of cylindrical gels with the dimensions of 1 cm diameter and 1 cm height were determined using Texture Analyzer (TA.XT*PLUS*, Hamilton, MA). A stainless steel cylinder probe with 40 mm diameter was used at a speed of 0.2 mm/s. Gel samples were compressed to determine gel strength and strain at the point of failure. Force versus deformation data were recorded. Then the data were converted to