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The effect of ionotropic gelation residence time on alginate cross-linking and properties

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ABSTRACT

The ability to engineer biocompatible polymers with controllable properties is highly desirable. One such approach is to cross-link carbohydrate polymers using ionotropic gelation (IG). Previous studies have investigated the effect of curing time on alginate cross-linking. Herein, we discuss a novel study detailing the effect of IG residence time (IGRT) on the cross-linking of alginate with calcium ions (Ca^{2+}) along with water migration (syneresis) and their subsequent impact on the pharmaceutical properties of alginate particles. IGRT was shown to have a significant effect on particle size, porosity, density, mechanical strength and swelling of calcium alginate particles as well as drug release mechanism. Furthermore, we describe a novel application of electron dispersive spectroscopy (EDS), in conjunction with Fourier Transform- infra red (FT-IR) spectroscopy, to analyze and monitor the changes in Ca^{2+} concentration during cross-linking. A simple procedure to determine the concentration and distribution of the surface and internal Ca^{2+} involved in alginate cross-linking was successfully developed.

1. Introduction

Ionotropic gelation (IG) or ionic cross-linking is the capacity of poly-electrolyte polymers to cross-link by counter ions (Patil, Chavanke & Wagh, 2012). This technique has been adopted for natural carbohydrate polymers to produce biocompatible and biodegradable products. Several polymers have been cross-linked using this technique, including alginates (Leong et al., 2016), gellan gum (Patil, Kamalapur, Marapur & Shiralshetti, 2011), chitosan (El-Mahrouk, El-Gazayerly, Aboelwafa & Taha, 2014), and pectin (Abouelatta, Aboelwafa, Khalil & El-Gazayerly, 2015).

In this work, sodium alginate was chosen as the model polymer to investigate. Alginate is an FDA-approved natural polymer derived from brown algae. It is widely used in food, biomedical, and pharmaceutical applications because of its biocompatible and biodegradable properties (Skaugrud, Hagen, Borgersen & Dornish, 1999). Alginate hydrogels, particles and microparticles are prepared by simple complexation with divalent cations such as calcium (Ca^{2+}). These complexes are safe and cheap to prepare and can be used in a variety of applications. Calcium alginate has been used as a biodegradable support for water decontamination reagents (Benhouria, Islam, Zaghouane-Boudiaf, Boutahala & Hameed, 2015; Jain, Garg, Kadirvelu & Sillanpää, 2015; Kuang et al., 2015) as well as scaffold for cell cultures (Cuadros, Erices & Aguilera, 2015). For instance, calcium alginate has also been used for drug delivery such as the parenteral delivery of chemotherapeutics (Pandey & Khuller, 2004) and topical drug applications such as wound healing dressings (Pankongadisak, Ruktanonchai, Supaphol & Suwantong, 2015). Calcium alginate is also used in the preparation of sustained release oral delivery systems such as floating (Nayak, Jain & Pandey, 2011), mucoadhesive (Adebisi, Laity & Conway, 2015) and colon targeted formulations (Bansal, Gulbake, Tiwari & Jain, 2016).

Alginate is a block copolymer of mannuronic acid (M), guluronic acid (G), and mannuronic-guluronic (MG) monomers. In the preparation of calcium alginate particles (CAPs) using the IG technique, sodium alginate solution is extruded into a solution containing

Abbreviations: AAP, acetaminophen; ANOVA, analysis of variance; ATR, attenuated total reflectance; BCS, biopharmaceutical classification system; CAP, calcium alginate particle; CSD, Cambridge structure database; DL, drug loading; EDS, electron dispersive spectroscopy; FTIR, Fourier-transform infrared; IG, ionotropic gelation; IGRT, ionotropic gelation residence time (IGRT); f_2, similarity factor; SGF, simulated gastric fluid; SIF, simulated intestinal fluid; XRPD, X-ray powder diffraction.

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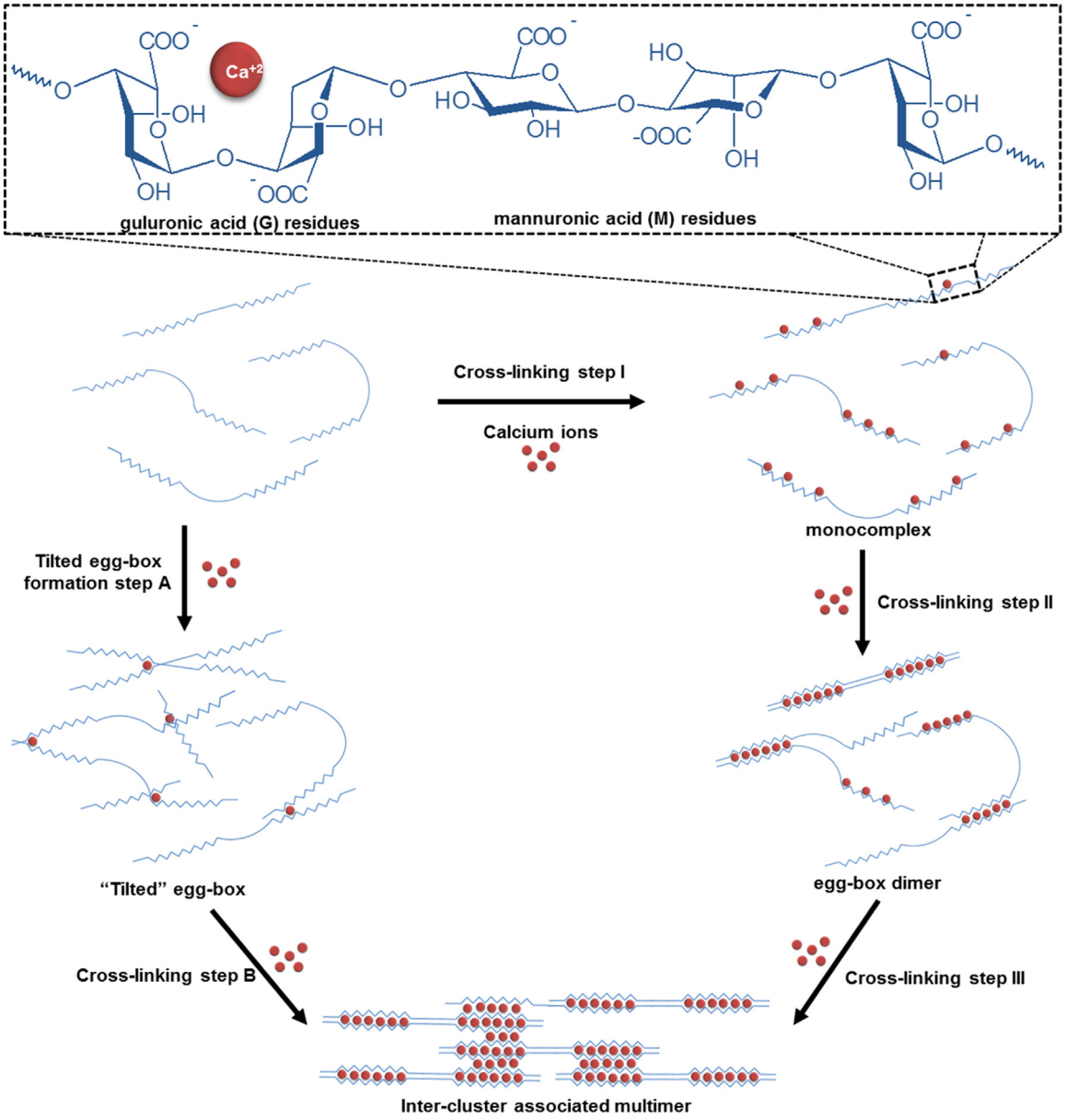

Fig. 1. Schematic diagram showing the steps involved in calcium ion induced cross-linking of the alginate as suggested by (right, steps I-III) Fang et al. (2007) and (left, steps A and B) Borgogna et al. (2013).

the divalent cation. These cations replace the sodium present in the polymer chains and initiate the crosslinking process. The egg-box model describing the cross-linking of alginates with divalent cations was first described by Grant et al. (Grant, Morris, Rees, Smith & Thom, 1973). Fang et al. (Fang et al., 2007) suggested that this process starts by the formation of a monocomplex, followed by an eggbox dimer. Finally, it forms inter-cluster associated multimers, which constitute the fully cross-linked form of calcium alginate (Fig. 1, steps I–III). Recently, Borgogna et al. (Borgogna, Skjåk-Bræk, Paolett, & Donati, 2013) opposed the idea of monocomplex formation and suggested the tilted egg-box model. They proposed that the process starts by the interaction of one calcium ion with monomeric guluronic acid units from two different alginate chains. This interaction leads to the formation of egg-box like structure; the tilted egg-box. However, these dimers are not parallel to each other, but tend to be placed almost perpendicular to each other (Fig. 1, steps A and B).

Previous work has studied the effect of the different parameters affecting IG and the corresponding physicochemical characteristics of the CAPs. These include the concentration and type of alginate with different viscosity grades and M to G ratios (Fang et al., 2007; Lemoine, Wauters, Bouchend'Homme & Préat, 1998), the concentration and type of complexing cation (Acartürk & Takka, 1999; Ouwerx, Velings, Mestdagh & Axelos, 1998; Takka & Acartürk, 1999), the method of extrusion, stirring speed and the method of drug loading (Fundueanu, Nastruzzi, Carpov, Desbrieres & Rinaudo, 1999; Reis, Neufeld, Vilela, Ribeiro & Veiga, 2006; Wang, Chen, Weng, Chen & Xie, 2004).

Previous studies have also investigated the effect of varying the curing time as a process variable in the preparation of CAPs (El-Kamel, Al-Gohary & Hosny, 2003; Kim & Lee, 1992; Lee & Min, 1996; Patel, Sher & Pawar, 2006; Rousseau, Le Cerf, Picton, Argillier & Muller, 2004; Šillerová, Komárek, Liu, Poch & Villaescusa, 2015; Smrdel et al., 2006). Furthermore, the effect of the type and concentration of alginate and cross-linking cation on particle deswelling