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Alginate: Applications in the modern world

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ABSTRACT

Alginate is a natural polysaccharide extracted from the cell walls of brown algae. Thanks to its biocompatibility, biodegradability, nontoxicity, and low cost, this biopolymer is widely applicable across various fields of biomedical science and bioengineering. Alginates are used as a gelling agent in food industry. Alginate hydrogels are an appealing scaffold material because of their resemblance with natural tissues. Consequently, alginates are widely used in tissue engineering and alginate gel beads as transport vehicles in drug delivery systems. Nonetheless, alginate hydrogels are used in nanotechnology to build artificial capillary blood vessels.

***Keywords**: alginate, biopolymer, hydrogel, gel beads, drug delivery, tissue engineering*

Introduction

Alginate (ALG), a naturally occurring biopolymer commercially extracted from brown seaweeds (*Phaeophyceae* such as *Fucus*, *Laminaria*, *Ascophyllum*) (Rinuado, 2014), has a variety of applications in the modern world of which some will be discussed in this short review. ALG polymers are a family of linear unbranched polysaccharides made up of (1→4)-linked β-D-mannuronic acid (M) and α-L-guluronic acid (G) (Fig. 1a) residues. The fact that M and G are C5 epimers results in a switch-over of the monomer chair conformation, giving rise to all four possible glycosidic linkages (Draget, 1997). Therefore, three types of building blocks appear in polymer: MM, GG, and MG (Fig. 1b). When ALG is added to an aqueous solution of multivalent cations (*e.g.*, Ca^{2+}, Ba^{2+}, Cu^{2+}), chelation occurs and ionic hydrogel forms. The selective binding of multivalent cations is one of the most important properties of ALG, which is the basis for gel formation, and the fact that sol–to–gel conversion of alginates is not peculiarly influenced by temperature. In the most commonly used hydrogel, calcium alginate (Ca-ALG), the strong interaction between calcium ions and sugar residues create junction zones in the ALG network, in which, calcium is embedded into the GG blocks forming so-called egg-box model (Fig. 1c). Thus, the G/M ratio often determines the physicochemical properties of the hydrogel (Balać et al., 2010; Tønnesen and Karlsen, 2002; Tønnesen and Karlsen, 2011).

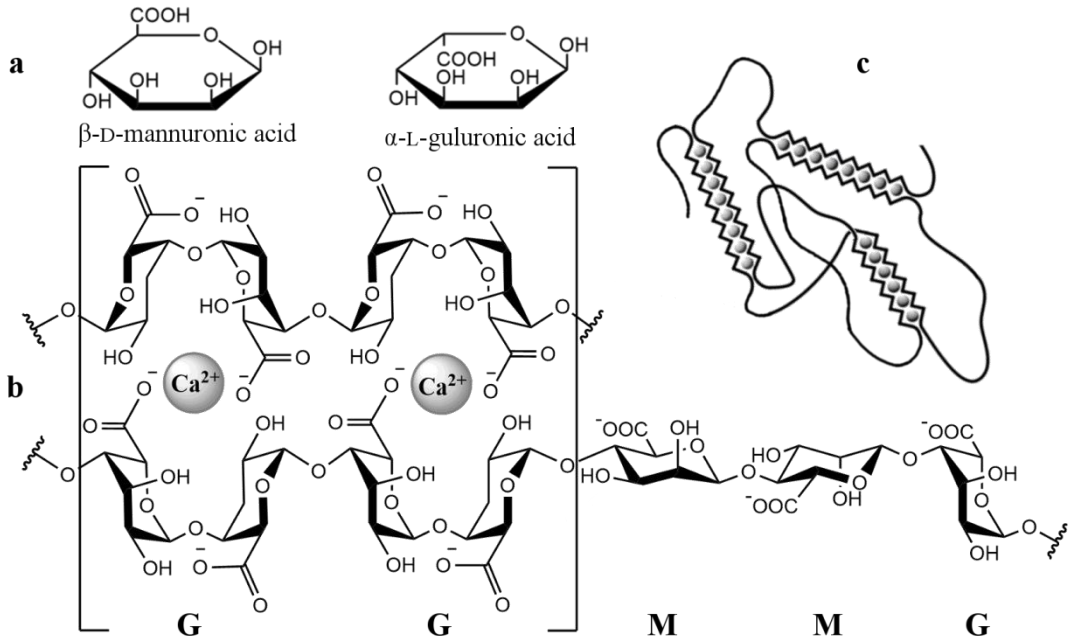

Figure 1. Monosaccharides (a), building blocks: GG, MM, and MG (b), and schematic crosslinking of Ca-ALG including the egg-box model (c).

Considering that ALG is generally regarded as safe by the U.S. Food and Drug Administration (FDA), it has been used commercially as a gelling agent in the food industry (Brownlee et al., 2009), pharmaceutical (Tønnesen and Karlsen, 2002), biomedical (Lee and Mooney, 2012), and personal care.

Preparation of alginate hydrogel

ALG gel beads are generally prepared by adding Na-ALG solution dropwise into an aqueous solution of $CaCl_2$. Gel strength and volume reduction of the beads increases with increasing concentration of the $CaCl_2$ solution up to 0.02M. For higher concentration of Ca^{2+}, the gel strength and volume reduction are approximately constant. The size of gel beads depends upon the type of ALG and the gelling conditions (Martinsen et al., 1989). Additionally, gelation could be activated by UV irradiation, as well. The approach involves a combination of an insoluble salt of the cation (*e.g.*, calcium carbonate, $CaCO_3$), an aqueous solution of ALG, and a photoacid generator. Upon exposure to UV light, the photoacid generator dissociates to release H^+ ions, which react with $CaCO_3$ to generate free Ca^{2+}. Photogellable ALG solutions are used for encapsulation of cells and calcium-sensitive biomolecules. Plus, the light-triggered gelation can be achieved in a local manner (Javvaji et al., 2011).

Alginate in drug delivery systems

ALG hydrogels are insoluble but swellable in an aqueous medium. Due to its moisture and resemblance with natural tissues, ALG hydrogel is an excellent candidate for drug delivery and tissue engineering (Ratner and Bryant, 2004; Tønnesen and Karlsen, 2002). ALG, being a polyanion, has the increased charge density giving rise to a greater mucoadhesion. In addition, ALG has the highest mucoadhesive strength in comparison to polymers such as polystyrene, chitosan, carboxymethylcellulose, and polylactic acid (George and Abraham, 2006).

The biocompatibility of ALG hydrogels heavily depends on the G/M ratio and the inner viscosity of the prepared hydrogel. ALG hydrogels, especially ALG beads, are being

used as delivery systems for bioactive peptides and proteins, genes, and a variety of drugs (Li et al., 2012).

Spherical beads are formed instantaneously when droplets of Na-ALG solution get in contact with the $CaCl_2$ solution. ALG beads have the ability to reswell. This property is responsive to the pH of the environment, so acid-sensitive drugs, taken orally, would be protected from gastric juice (pH = 1.5 – 2.0), but once dried particles enter the small intestine (pH = 7.4), the beads reswell to their original size and function as matrices for controlled release of encapsulated drugs (Yotsuyanagi et al., 1987). Due to the adherence of ALG particles to the mucosal tissues, protein transport time is prolonged and the drug is localized, which improves drug bioavailability and effectiveness (George and Abraham, 2006).

ALG scaffolds are able to release encapsulated proteins by two mechanisms: (1) diffusion of the protein through the porous ALG matrice (Fig. 2) (pores being 5–200 nm in diameter), and (2) degradation of the polymer network. The increase of the abundance of alginate in the beads lowers the rate of diffusion of the proteins from the matrix. However, small molecules such as glucose and ethanol diffuse uninterrupted from the gel. Therefore, cell encapsulation methods began to thrive, especially the encapsulation of hormone-producing cells or recombinant cells for the treatment of diabetes mellitus, liver diseases, parathyroid disorders, and various neurological disorders (Gambotz and Wee, 1998).

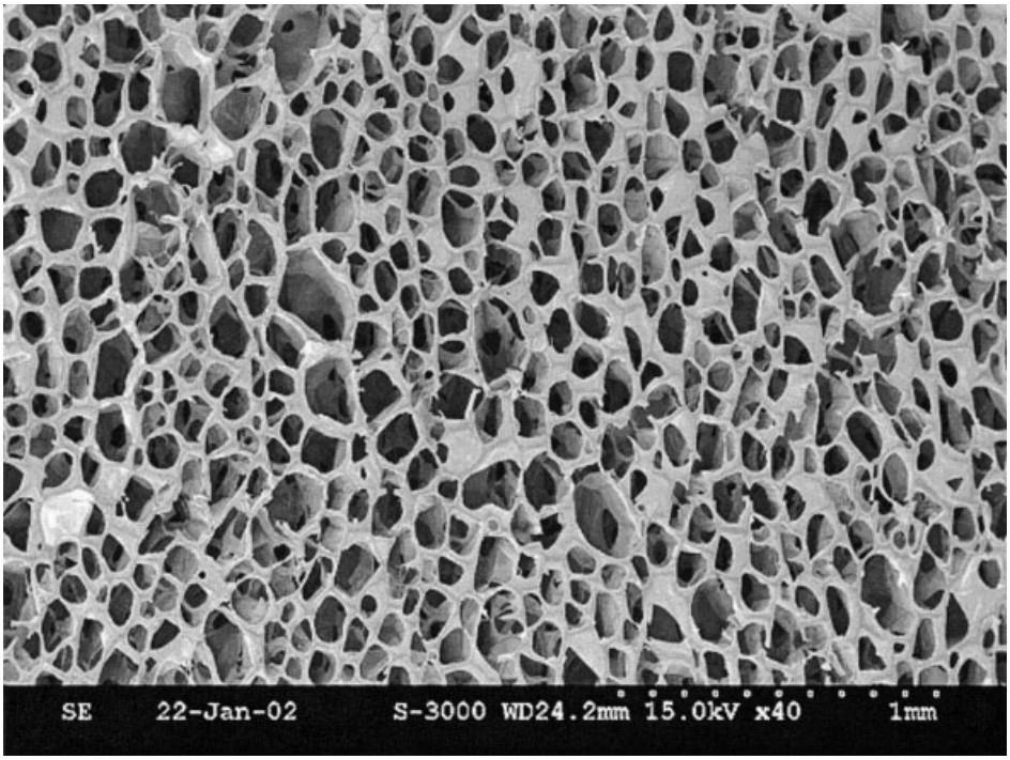

Figure 2. Typical top surface morphology of pure alginate scaffold (3% alginate, crosslinker: 0.03*M* $CaCl_2$, freezing temperature: – 40°C). Original magnification: x40.

Alginate in tissue engineering

The general objective of tissue engineering is to forge a structure that matches the physicochemical properties of the natural tissue (Gambotz and Wee, 1998), and eventually to fabricate living replacement parts for the body. Due to their mechanical properties and biocompatibility, ALG scaffolds are highly qualified candidates for the field. For example, the regeneration of bone after tissue loss is accomplished by using interconnected, highly porous ALG/hydroxyapatite composite scaffolds (Fig. 3), whose structure is similar to the bone tissue structure. Besides, ALG scaffolds are used as a space-filling agent because they provide bulking and prevent adhesions, or function as bioadhesives (Drury and Mooney, 2003; Lin and Yeh, 2004; Venkatesan et al., 2014). Therefore, ALG scaffolds are applicable in soft-tissue engineering, as well.

The advancement of nanotechnology has made possible to use ALG hydrogels in micro and/or nanodevices because gelation occurs even at such scale. As a result, artificial capillary blood vessels are built using the inkjet printing technique (Henmi et al., 2007), as well as *in situ* forming injectable hydrogel, a suitable delivery carrier for encapsulated stem cells for soft tissue regeneration (Deepthi and Jayakumar, 2017).

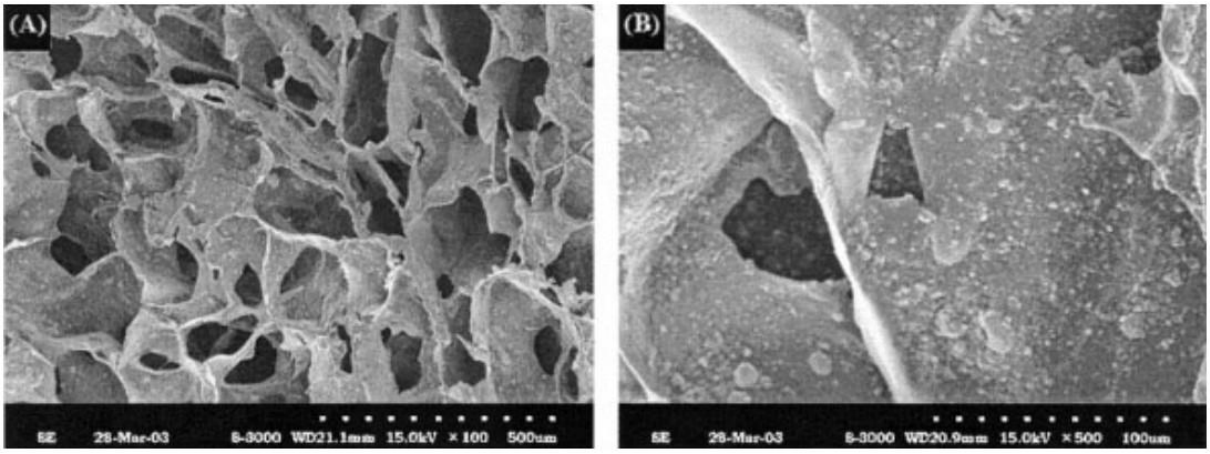

Figure 3. Surface morphology of 75/25 alginate/HAP composite scaffolds (3% alginate, crosslinker: 0.03*M* $CaCl_2$, freezing temperature: – 40°C). Original magnification: A = x100; B = x500.

Conclusion

This short review has a mission to point out the significance of alginates in the modern world, especially the numerous applications in the fields of biomedical science and bioengineering. Considering the favorable physicochemical properties and low price, this biopolymer remains a great candidate for further interdisciplinary studies.

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