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Review

# Advances in fabricating spherical alginate hydrogels with controlled particle designs by ionotropic gelationas encapsulation systems

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ABSTRACT

Alginate is a biopolymer that has exceptional gelling properties, which allow easy gel formation under safe and mild conditions. Consequently, it is often used to encapsulate a variety of cargos, such as cells, enzymes, and lipids, and is typically employed as a model to study hydrogel-based encapsulation systems. Since the first use of alginate in the encapsulation field in the 1970s, many methods have been developed to produce alginate hydrogel particles of different sizes, structures, and morphologies. This review provides an overview of the current progress in the fabrication of alginate hydrogels with various particle designs, including a discussion of dispersion techniques to pre-template alginate particles, gelation mechanisms, considerations in selecting suitable fabrication methods, and future directions.



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## Introduction

Gel-forming polymers from natural sources represent an important class of biomaterials for encapsulation applications because of their renewability, biodegradability, biocompatibility, and non-toxicity. Among this class of polymers, alginate has received much attention in the literature (see Fig. 1), likely because it can form hydrogels primarily by ionotropic gelation with divalent ions (e.g., $Ca^{2+}$) at room temperature, thereby allowing immobilization to be performed under mild and safe conditions. Furthermore, the most basic particle design of alginate hydrogels (i.e., beads) can be produced using simple equipments, e.g., beakers and syringes, and the encapsulation process can be performed in virtually any laboratory.

Aside from their advantages in the production method, alginate hydrogels possess outstanding physical properties. They are thermally stable and can form gels very rapidly, even in the presence of high solid concentrations (e.g., up to 30% w/v). The mechanical, mass transport, and disintegration properties of alginate hydrogels are also tunable. Furthermore, alginate hydrogels have small-sized pores (5–200 nm) (Martinsen, Storrø, & Skjåk-Bræk, 1992) and are hydrophilic, making them suitable for encapsulating large molecules or hydrophobic materials at high efficiencies, generally higher than 90% (Chan, 2011; Lemoine, Wauters, Bouchend'homme, & Préat, 1998). Depending on their solubility in water, some small hydrophilic molecules, such as melatonin, aspirin, cimetidine, sodium salicylate, and glucose oxidase, have also been successfully encapsulated, though at lower encapsulation efficiencies (Lee, Min, & Cui, 1999; Blandino, Macías, & Cantero, 2001).

To date, alginate has been used for encapsulating various cargos such as living cells, protein drugs, enzymes, food ingredients, volatile compounds, and catalysts. The immobilized systems have been employed in diverse applications including tissue engineering, controlled drug delivery, biocatalysis for chemicals production, stabilization of food ingredients, adsorption of pollutants, and energy storage. Academic interests largely motivate many of these applications, but many industrial companies have begun to offer encapsulation solutions and services over the last decade.

Alginate is a hydrophilic biopolymer derived from brown seaweeds and is composed of (1–4)-linked β-D-mannuronic (M) and α-L-guluronic acid (G) residues (Martinsen, Skjåk-Bræk, & Smidsrød, 1989). This review, however, does not discuss the chemistry or properties of alginate or its derivatives because these topics have been covered in detail elsewhere such as in the recent review paper by Lee and Mooney (2012). In contrast, we provide an overview of alginate hydrogel particle designs formed by various ionotropic gelation process routes. Many methods have been developed to produce alginate hydrogel particles of different sizes and morphologies to suit the needs of various applications. The synthesis routes to form alginate hydrogel particles generally consist of two processing steps i.e., dispersion of the alginate sol, followed by gelation of the sol with cations. Advances in dispersion and gelation methods over the past 10 years have enabled the production of particles that are both small and uniform or complex in their particle morphology. We systematically categorize and review these methods and compare them with respect to particle size, size distribution, and economics and efficiency of production. The shortcomings of the existing methods are discussed, where possible, with opportunities for further research in the field.

## Particle size and morphology

The term 'particle' is used broadly throughout this paper without referring to any specific size or morphology. The specific terms used to describe the particle size and morphology of alginate hydrogels are described in Fig. 2. The classic morphologies are 'beads' and 'capsules'. Beads are defined as spheres that have diameters larger than 1000 μm; the immobilized cargo, either hydrophilic or lipophilic, is typically dispersed throughout the polymer matrix within the beads. Capsules, conversely, are spheres that comprise a distinct membrane that engulfs a liquid core containing the cargo.

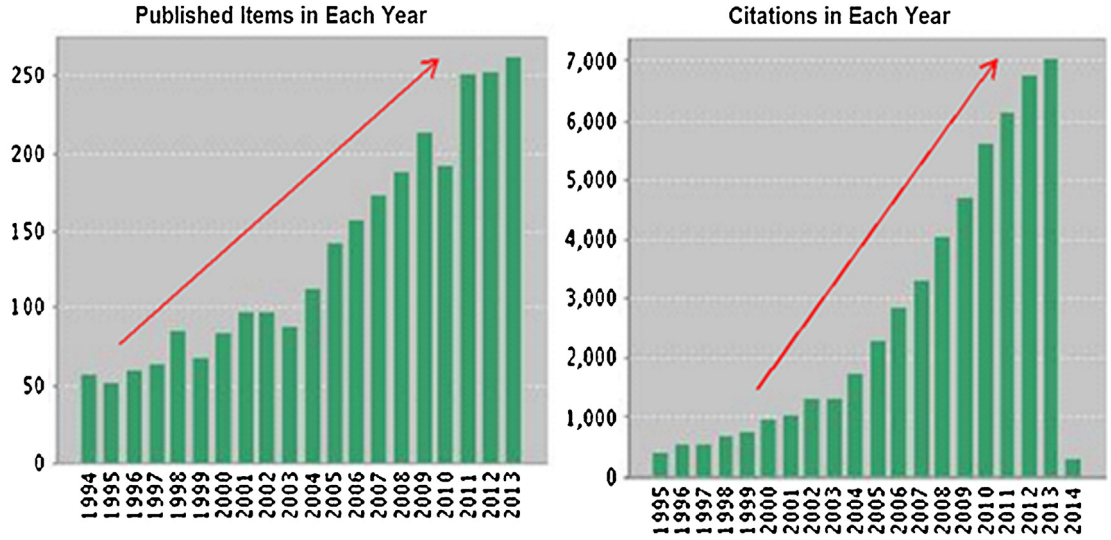


**Fig. 1.** Publication and citation data on alginate over the past 20 years (*source:* Web of Knowledge). Note, the data were obtained using keywords in the topic and search criteria as follows: {(Alginate) AND (Encapsulation OR Immobilization) AND (Bead OR Capsule OR Particle OR Sphere)}.

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