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Preparation methods of alginate nanoparticles

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ABSTRACT

This article reviews available methods for the formation of alginate nano-aggregates, nanocapsules and nanospheres. Primarily, alginate nanoparticles are being prepared by two methods. In the "complexation method", complex formation on the interface of an oil droplet is used to form alginate nanocapsules, and complex formation in an aqueous solution is used to form alginate nano-aggregates. In a second method w/o emulsification coupled with gelation of the alginate emulsion droplet can be used to form alginate nanospheres. We review advantages and disadvantages of these methods, and give an overview of the properties of the alginate particles produced with these methods.

Contents

1. Introduction

The first alginate particles for encapsulation purposes were developed in 1980 [1]. Since then much research has been performed on the development and application of alginate particles, resulting in alginate being one of the most commonly applied materials for the formation of hydrogel (micro) particles nowadays [2–5]. Alginate can easily be gelled with multivalent cations under gentle conditions, making it applicable for the entrapment of sensitive materials.

Most of the gelled alginate particles described in literature have a diameter larger than 100 μm. Alginate particles much smaller than that (<1 μm) have several advantages over such larger alginate particles. Small particles have a higher mechanical strength and a larger specific surface area. They can easily flow through narrow nozzles and channels which would be blocked by larger particles. Especially in drug delivery, nanoparticles have attracted considerable attention and have several advantages over micron-sized particles [6–14]. However the formation of nanoparticles from alginate is less common, and synthetic polymers like poly(lactic acid) (PLA), poly(glycolic acid) (PGA) and poly(lactide-co-

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glycolide) (PLGA) have received significantly more attention in the literature [13].

In this review, the focus will be on the formation of alginate nanoparticles. First some general chemical and physical properties of alginate and different types of alginate bulk gels are discussed. This is followed with a brief overview of methods to prepare alginate *microparticles*. Then the different methods for the formation of alginate *nanoparticles* are discussed. Finally conclusions and a discussion of remaining challenges are given.

1.1. Alginate

Alginate has been extensively reviewed with respect to its physical and chemical properties, and its use in the formation of (micro)particles and bulk gels [15–25]. Alginate is non-toxic, biodegradable, low in cost, and readily available, and has been found to be a mucoadhesive, biocompatible, and non-immunogenic substance. Alginate is an anionic polymer, produced by brown algae and bacteria, and consists of α-L-guluronic acid (G) and β-D-mannuronic acid (M) residues, linearly linked by 1,4-glycosidic linkages (Fig. 1). The composition and sequence of the G and M residues depend on the source of the used algae, and influence the properties of the alginate. Alginate can also be chemically modified to alter its properties [26,27].

1.2. Alginate hydrogels

Alginate hydrogels can be prepared through chemical and/or physical crosslinking of the polymer chains. The physicochemical properties of the alginate gels are dependent on the type of crosslinking, crosslinking density, and molecular weight and composition of the alginate [24]. Also the presence of complexing agents such as phosphate and citrate is an important factor [28]. The most common method for the formation of alginate gels is by ionic cross-linking with multivalent cations. This method can take place under gentle conditions, making it ideal for the entrapment of sensitive materials. The gelation of alginate occurs by an exchange of sodium ions from the guluronic acid (G) blocks with multivalent cations, and the stacking of these G blocks to form a characteristic "egg-box" structure (Fig. 2) [24,29]. Each chain can be linked with many other chains, resulting in the formation of a three-dimensional gel network. These gels can have water contents greater than 95% [23] and can be heat treated without melting [28]. Gels prepared from alginates with a high G content tend to form stronger, stiffer, more brittle and more porous gels. It has also been reported that the higher the G content, the greater the restriction to solute transport [19,21]. Conversely, high M content results in gels which are more elastic and weaker [24,30].

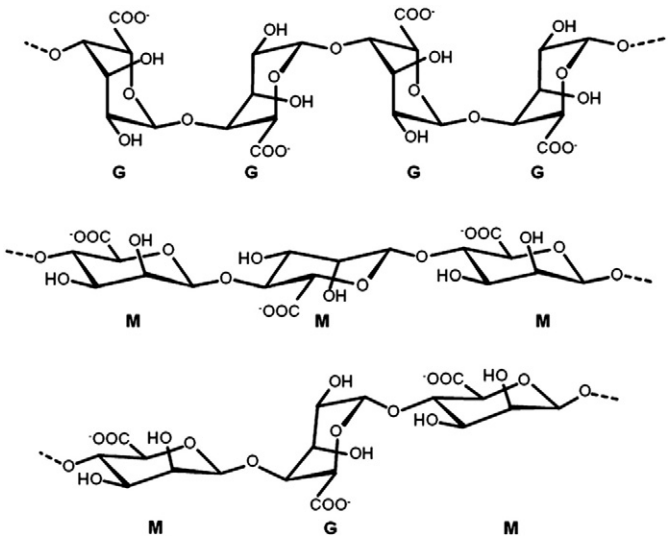

Fig. 1. Chemical structures of G-block, M-block, and alternating block in alginate. [27].

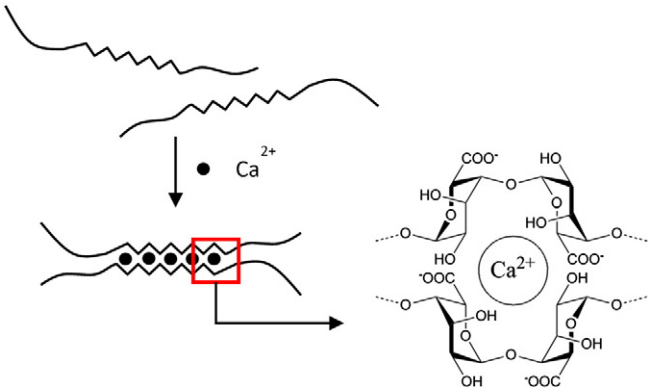

Fig. 2. Formation of an alginate gel by calcium cations, resulting in "egg-box" calcium linked junctions.

Various cations show different affinity for alginate, whereof calcium is most frequently used for alginate gelation, but calcium does not form the strongest bonds with alginate [18,30,31]. Monovalent cations and Mg^{2+} ions do not result in the formation of a three-dimensional gel network [23]. The gelation of alginate solutions with cations can occur through so-called external gelation, internal gelation and gelation upon cooling [18].

For external gelation alginate is often dripped into a bath containing cations, such as a calcium chloride solution. The cations diffuse from the continuous phase to the interior of the alginate droplets, and form a gelled alginate matrix, from the outside migrating to the center of the alginate droplet [32–34]. The method is therefore also referred to as "diffusion method".

Internal gelation, also referred to as "internal setting" or "in situ gelation", makes use of a water insoluble calcium salt, like $CaCO_3$, which is mixed with the alginate solution. Calcium ions are subsequently released from the interior of the alginate phase by lowering the pH of the system and/or increasing the solubility of the calcium source, resulting in the formation of an alginate gel.

The third method uses an alginate solution with a calcium salt at elevated temperatures (90 °C), which is then allowed to set through cooling [35]. The elevated temperature in this method makes it less gentle and is unsuitable for thermally labile material.

The external gelation or diffusion setting is characterized by fast gelation which generally results in a final gel that is inhomogeneous. The diffusion setting will create a fast gelling zone moving from the surface of the gel to the center, which results in a high alginate concentration at the surface and a low one at the center. Using a high molecular weight alginate and presence of non-gelling ions will result in a more homogeneous gel [28].

Internal gelation results in homogeneous gels when the calcium source remains evenly distributed during gelation [24,28,36–38]. The molecular weight of the alginate has a larger influence on the gel strength than in external gelation. Alginate gels prepared through internal gelation tend be more prone to syneresis than external set gels [28]. Alginate gels prepared through internal gelation and external gelation differ in several properties such as matrix strength, stiffness, pore size and permeability [32–34].

Ionically cross-linked alginate gels can be dissolved by the release of the multivalent cations through exchange reactions with monovalent cations and magnesium, and complex anions such as phosphate, citrate, and lactate, which have high affinity for calcium ions [19,21,36].

Other chemical or physical cross-linking methods have been developed as well. Alginate precipitates at pH values below the pK_a value and using controlled conditions can result in the formation of alginate acid gels [28,37,38]. Covalent cross-linking has also been developed for alginate gels, together with the thermal gelation and also cell cross-linking of modified alginates [24].