Alginate Application in Drug Delivery

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Alginates are generally used in the food, beverage, cosmetic, paper, textile printing, and pharmaceutical industries. They have been utilized as stabilizers, thickeners, emulsifiers, and hydration and gelling agents. The main use of alginate in the biomedical industry is mainly focused on hydrogels used in wound healing, drug delivery, and tissue regeneration. The broad range of applications is due to its biocompatibility, low toxicity and relatively low-cost consumption, and structural similarity to the extracellular matrices of living tissue.

alginate drug delivery

1. Alginate Hydrogel

Alginate hydrogels are biocompatible and structurally identical to the macromolecular-based component of the biological body. Hydrogels are defined as three-dimensional networks in which hydrophobic polymers chains are crosslinked together [1]. The crosslinking of alginates, specifically, can be conducted via ionic, covalent, and cell pathways as well as by free radical polymerization [2][3]. However, ionic crosslinking is the typical way to synthesize alginate gels, and calcium has been traditionally used to establish crosslinking. The tendency to use ionic crosslinking is supported by the fact that it offers an adequate method for active substance entrapment without affecting their bioactivity [4].

A critical factor in controlling the gelation process using divalent cations is the gelation rate. Gel uniformity and greater mechanical integrity are expected from a slower gelation system [5]. When crosslinking alginates, calcium carbonate and calcium sulfate have shown different gelation rates [6]. With a rapid gelation rate, the calcium chloride is suitable for ionic crosslinker for a bioencapsulation scheme, whereas others are more favored in tissue engineering scaffolds. The gelation rate also depends on the temperature; low temperature reduces the Ca^{2+} reactivity, leading to low gelation rates, well-ordered network structures, and improved mechanical properties [2].

On the other hand, the alginates' M/G ratio and molecular weight contribute to the variation of the physicochemical properties of their ionic-crosslinked gel. The geometries of the G-block, M-block, and alternating regions are different due to particular shapes and modes of linkage in the alginate sequence. Thus, their intermolecular crosslinking with divalent ions is dissimilar and gives other gel characteristics. A higher content of G-block results in higher tensile strength and modulus and more extensibility than for alginates richer in M-blocks [7]. In addition, a rheological study of high molecular weight alginate fluid gels showed rapid gelation kinetics and higher viscosities than lower molecular weight [8]. The alginate source and the gelling ion conditions (type and concentration) affect

the gel stability and permeability. A study on calcium, barium, and strontium ions has been conducted, forming alginate microbeads [9]. These three different cations reacted differently with the G- and M-blocks of alginate, resulting in diverse stability, permeability, gel strength, and distribution of alginates in the gel beads.

Besides ionic crosslinking, many alternative approaches to produce alginate gels have been investigated. Alginate can be covalently crosslinked using carbodiimide chemistry, and one study found that the crosslinker type and the crosslinking density adequately affect hydrogel properties [10]. The crosslinking density affected the mechanical properties of hydrogels, and the type of crosslinking molecules influenced the swelling properties. Another representative strategy prompting the covalent crosslinking in alginate is free radical polymerization. Alginate-methacrylate hydrogels can be prepared through photopolymerization, obtaining mechanical properties that are dominated by the molecular conformation and electron density of the methacrylate reactive groups [11]. Nevertheless, if the alginate polymer chain's surface is decorated with cell adhesion ligands, cell cross linking most likely also produces alginate gels [12].

The properties of alginate hydrogels, such as high-water content, nontoxicity, soft consistency, biocompatibility, and biodegradability, make them sufficient candidates as drug carriers. As reported previously, alginate hydrogel could synthesize into nanogel, and it has good stability in biological fluid because of the low deriving for aggregation [13]. An alginate nanogel loaded with gold nanoparticles creates a thermos-responsive platform suitable for chemo-photothermal therapy for breast cancer [14]. Another study also developed a pressure trigger controlled drug released from alginate-cyclodextrin nanogel [15]. This carrier manages to enhance the apoptosis mechanism for colon cancer drug delivery. An improved drug loading efficiency of alginate nanogel for cancer therapy can be achieved using additional keratin to create a composite platform [16].

2. Alginate Ester

Alginate ester is synthesized through esterification. Esterification is the earliest functionalization of alginate, and it is generally carried out in non-aqueous systems. This functionalization could perform to both available functional groups, either carbonyl or hydroxyl. An additional catalyst is needed for esterification of the hydroxyl groups for a more selective reaction [17].

A full chemoselective carbonyl alginate ester was introduced with the use of tetrabutylammonium (TBA) salt of alginate [18]. This amphiphilic alginate is suggested for use as an amorphous solid dispersions (ASDs) matrix. The presence of alginate esters, ethyl, butyl, and benzyl are aimed at enhancing drug solubility. The introduction of butyl groups to alginate through esterification forms hydrophilic alginate without losing their gelation ability in the presence of calcium chloride [19]. By using the same functionalization method, a methyl alginate ester was synthesized and used as an excipient for direct compression in immediate drug-release tablet production [20]. Another study created a nanoparticle platform based on oleate alginate ester for curcumin delivery [21]. Alginate is active with formamide so it can actively react with methyl oleate; alginate ester is formed after 48 h of reaction, and the excess formamide can be removed with soxhlet apparatus.

The attachment of the hydrophobic moieties on the alginate backbone creates a micelle carrier system. Such a system is one way to enhance the solubility of poorly water-soluble drugs and drug loading encapsulation, and is a controlled release mechanism [22]. However, further investigation is necessary to improve the solubility enhancement factor and to find a compatible way to facilitate ASD formation. Moreover, the development of a specific esterification method is needed to create a tunable hydrophobicity–hydrophilicity balance characteristic [18].

3. Alginate Dialdehyde

Alginate cannot degrade in mammals due to a lack of alginate-degrading enzymes [23]. Ionically crosslinked alginate hydrogels, on the other hand, can be dissolved by ionic exchange reaction, but the high molecular weights (>50 kDa) of the parent alginate restrain the renal clearance. To address the limitation, alginate dialdehyde (ADA), which Malaprade first reported, has been widely investigated [24][25][26]. This alginate derives from partial oxidation of alginate chains, involving C_2-C_3 bond cleavage and transforming into an open ring containing two aldehyde groups. This functionalization is selective modification of the hydroxyl moieties. ADA has a lower molecular weight and is more soluble in aqueous media. Its stiffness and persistence length decreases with an increase in the degree of oxidation [27].

ADA consists of multiple aldehyde groups, a reactive group that can form covalent bonds with free amino groups in gelatin, and chitosan. The development of Schiff's base crosslinking hydrogels between ADA and polymer containing free amino groups has been investigated [28][29]. A study found that the degree of crosslinking of ADA/PEG(polyethylene glycol)-gelatin hydrogels are higher than ADA/PEG-chitosan hydrogels [30]. This degree of crosslinking is defined as the number of groups that interconnect two materials, generally expressed in mole percent. This can be determined by trinitrobenzene sulfonic acid (TNBS) assay or ninhydrin assay [29][31]. Furthermore, the rheological, degradation, and comprehensive properties of the ADA/PEG-chitosan hydrogel are suggested to be more suitable for the self-crosslinking injectable scaffold.

The synthesis of hydrogels derived from ADA and gelatin has been reported; the crosslinking between ADA and gelatin was increased by increasing the degree of oxidation of ADA [32]. Such in situ forming hydrogel is used as wound dressing material; it is molded in accordance with the wound shape to enable conformability of the dressing for their application [33]. The advantage of alginates as a wound dressing is the ability to absorb excess wound fluid and maintain physiological moisture and an aseptic environment [34]. Another study successfully performed bone regeneration with RGD-alginate and found that the alginate's system showed an excellent bone formation ability [35]. The application of injectable hydrogel from ADA and gelatin for meniscal injury treatment has also been investigated [36]. Moreover, the same hydrogel could serve as a drug delivery vehicle in the formed nanogel and successfully delivered curcumin as an active ingredient [37].

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