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Calcium alginate hydrogel beads with high stiffness and extended dissolution behaviour

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ABSTRACT

Alginate hydrogel bead has been widely explored as a vehicle for controlled delivery application due to its non-toxicity, renewability, and ease of formation. However, alginate hydrogel beads are known to have a low stiffness, i.e., Young modulus <1 MPa, and a short dissolution time of between 1 h and 2 h in gastrointestinal fluid. This study aimed to fabricate calcium alginate hydrogel beads with desired properties like high stiffness and extended dissolution behaviour. A temperature-controlled extrusion–dripping method incorporating an immiscible interphase column was used to produce the ultra-high concentration (UHC) calcium hydrogel beads directly from unmodified alginate solution. The UHC beads have an extraordinary internal structure with thick calcium-alginate matrices and large pores in between the matrices. The Young's modulus value of UHC calcium alginate beads was 3.6 MPa, which was approximately 8 times higher than the normal calcium alginate beads. The release profile for the model drug (i.e., methylene blue) encapsulated in UHC beads was found to be extended to 4 h at 80% of drug release (t_{80}). The kinetics of drug release fitted well with the Korsmeyer–Peppas model ($r^2 \geqslant 0.99$) and followed the non-Fickian mechanism. These findings show that the preparation of calcium alginate beads featuring high stiffness and extended dissolution profile can be achieved without any chemical modification or additives. The UHC calcium alginate bead holds excellent promise as an encapsulation carrier of drugs or food used in controlled delivery applications.

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1. Introduction

Alginate, a type of hydrophilic biopolymer extracted from brown seaweed, consists of β-D-mannuronic acid (M) and α-L-guluronic acid (G) monomers. The uronic-acid-based monomers are joined together by 1,4-glycosidic linkages, and they exist in either homopolymeric (M- or G-residues) block or heteropolymeric (random arrangement of M and G residues) block [1]. The European production of alginate, mostly in Norway and France, is estimated at 10 thousand tonnes annually [2]. The alginate market in Europe is driven by the growing demand for sodium alginate in various industrial applications, particularly the food and pharmaceutical industries. In the past two decades, alginate has emerged as one of the most popular

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encapsulation materials for controlled delivery applications. Alginate is able to form hydrogel easily and safely upon the addition of divalent cations, such as Ca^{2+}, which bind to the carboxylates in the G-blocks to form the 'egg-box' structures [3].

However, alginate hydrogel beads are known to have low mechanical strength (i.e., Young's modulus ranging from 0.2 MPa to 0.5 MPa) and they can only withstand the deformation at a compression force up to 0.4 N [4,5]. It was reported that the alginate hydrogel beads that are compressed to 50% of their initial diameter will be deformed permanently [4]. Alginate hydrogel beads with low mechanical strength may be damaged during the production and application of the beads. For instance, during the transit of alginate hydrogel beads in gastrointestinal tract, the beads can be easily crushed by the contractile force of the stomach and small intestine, which can be as high as 1.9 N and 1.2 N, respectively [6,7].

In addition, alginate hydrogel beads have a very short dissolution time (i.e., between 1 h and 2 h) when they are exposed to the intestinal fluid [8,9]. Thus, alginate beads can only be applied in short-term release applications. Alginate hydrogels with a prolonged dissolution time are desirable for controlled release of drugs, such as pain relievers, anti-depressants, anti-hypertensive drugs or photosensitizer.

Many studies have been conducted to improve the mechanical strength or to extend the dissolution profile of the alginate beads. For instance, the mechanical strength of alginate beads was increased by 55% after coating the beads with chitosan [10]. The Young's modulus of alginate beads were increased by 35% after incorporating halloysite nanotubes fillers into the beads [11]. The alginate beads that were covalently crosslinked with polyacrylamide were 42 folds stronger than the pure alginate beads [12]. Alginate beads could also be treated with organic solvents to improve the rigidity of beads by 11 folds [13]. On the other hand, the drug release from alginate beads could be extended up to 55 h after the alginate polymer was modified hydrophobically [14]. All the above mentioned methods involve either a chemical treatment or the use of additives, which may give rise to safety concerns due to the use of organic solvents, toxic crosslinkers or initiators. Furthermore, these methods can only improve one aspect of the beads' properties (i.e., mechanical strength or dissolution rate), while some others gave only a marginal enhancement on the mechanical strength or the dissolution time of the beads.

Here we propose a facile and safe method to produce calcium alginate beads with an improved mechanical strength and an extended dissolution time. The calcium alginate beads were formed by using alginate solution at an extremely high concentration (i.e., 10% w/v) and high viscosity (i.e., 353,000 mPa s). The viscosity of alginate solution was more than 1000 fold of the viscosity typically applied (approximately 300 mPa s) in the production of calcium alginate beads via a conventional extrusion–dripping method [15]. It is well known that a highly viscous feed solution can be problematic for the production of alginate beads using this method. The viscous solution extruded from the nozzle tip form a long liquid thread. Before contacting the gelling bath, the detached liquid thread resists transformation into a spherical droplet, thus causing the formed bead resemble the shape of a tadpole. In many applications, especially in drug delivery system, spherical calcium alginate beads with uniform size are desirable due to their well-defined geometry that allows a reproducible and controllable drug release profile.

In this work, we developed a temperature-controlled extrusion system incorporating an immiscible interphase column to fabricate alginate beads at ultra-high concentration (UHC) from an alginate solution with a viscosity of 353,000 mPa s at room temperature. The interphase column consists of an oil phase as the top layer and a water phase containing calcium chloride ($CaCl_2$) as the bottom layer. The role of the oil phase was to slow down the descent of the detached droplets and allow the droplets to have sufficient time to transform into a spherical shape before contacting the $CaCl_2$ solution at the bottom phase. The feasibility of fabricating the spherical UHC calcium alginate beads was studied. The sphericity of the beads produced at varying stirring speed and $CaCl_2$ concentration in the interphase column was determined. The physicochemical and mechanical properties of the UHC alginate beads were determined, including their internal structure, the Young's modulus and the dissolution time. Finally, the potential of the UHC alginate beads in controlled-release of a model drug, methylene blue, was evaluated using an *in vitro* system. Methylene blue is a hydrophilic drug used in clinical applications to treat methemoglobinemia [16]. Methylene blue is also applied as photosensitizer in photochemotherapy for tumour tissues treatment [17,18].

2. Materials and methods

2.1. Materials

Manugel GHB sodium alginate with M/G ratio of 0.59 was used in this study (FMC Biopolymer, U.K., batch no.: G5707201). Calcium chloride dihydrate of analytical reagent grade was purchased from Fisher Scientific, UK. Methylene blue, monobasic sodium phosphate and dibasic sodium phosphate were purchased from Sigma–Aldrich, USA. Refined palm olein (Lam Soon Edible Oils Sdn. Bhd., Malaysia) was used as the immiscible top-phase solution in the interphase column.

2.2. Preparation of alginate solution

The alginate solutions were prepared by dispersing sodium alginate in distilled water. The solutions were stirred for 1 h at 1000 rpm using a mechanical stirrer. In this work, the alginate solutions were prepared at two different concentrations, namely at 2% w/v for the formation of beads serving as the control (i.e., designated as 'normal beads') and at 10% w/v for the production of UHC alginate beads. It is worth mentioning that alginate solution of 2% w/v is normally used in a typical

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