Immobilization of Analgetic AB-101 into Calcium Alginate Gels

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Abstract

A new analgetic drug AB-101 has been immobilized into Ca^{2+}-alginate gel beads with average diameter of 1 mm. A series of the alginate gel contains with various mannuronic/guluronic (M/G) ratios has been chosen to control the diffusion of the drug. Release of the drug from the alginate gel beads into physiological solutions consisting of sodium ions has been examined. A discontinuous time of the Fickian diffusion of the drug depending on M/G ratio was followed by a burst release of the remaining drugs. The burst release was due to a swift disintegration of Ca^{2+}-alginate with exchange on sodium ions. The preceding discontinuous lag time promotes a free dissociate exchange of sodium-calcium ions in M units, while the burst disintegration leads to fast dissociation of G units. The lag time can be control by M/G ratio of Ca^{2+}-alginate gels. The lag time increases if a content of the M units decreases. The increase of M units was led to more extensive swelling of the gel beads. Such way could be promising for a controlled drug delivery or the use in implants with controlled drug effect.

Introduction

Polymers have found applications in virtually every discipline of medicine, ranging from plain pharmaceutics and extracorporeal devices to intricately designed implants and organs. Polysaccharides constitute an important component of life matter. Polysaccharides display a perfect biocompatibility and biodegradability, which are the basic characteristics for polymers used as biomaterials [1]. The alginates is a natural copolymer composed of D-mannuronic acid (M) and L-guluronic acid (G) arranged in MM and GG blocks interrupted by regions of more random distribution of M and G units [2]. Due to the presence of carboxylate groups, alginate is a polyelectrolyte at neutral pH, with one charge per repeating unit in the coil conformation. Calcium alginate has been one of the most extensively investigated biopolymers forming gels in the presence of divalent cations at concentration of > 0.1% w/w. Specific intermolecular cooperative interactions occur between calcium and G blocks owing to the buckled ribbon structure of the polyguluronic acid, which is so-called "egg-box" junction zones. The rigid structure and large pore size of the gels are useful for the encapsulation of drugs, enzymes, and proteins [3-6].

With the aim of the development of implants with prolong analgetic action; the calcium-alginate gel beads as perspective implantable biomaterial have been prepared. The article is describing the release mechanism of analgetic drug from the alginate gel into sodium-containing medium.

Experimental

Sodium alginate was dissolved in deionized and distilled water at 2.0 wt.%. The ratio of mannuronic acid to guluronic acid residues was 1.05 (A1.0), 1.3 (A1.3), and 1.8 (A1.8) respectively. Drug AB-101 (0.01 mg) as a model drug was added to 25 mL of the resulting alginate solution and dissolved completely with stirring. The resulting solution (20 mL) was filtered through a syringe filter unit (0.45 μm, Milex-HV, Millipore, Ireland). It was then dropped into 100 mL of mildly agitated 0.1M $CaCl_2$ solution using at a drop rate of 1.0 mL/min the needle tip (0.65×25 mm). The bead diameter was measured and expressed as an average value of 5 beads. The standard deviation of the bead diameters was always within 5.0% of the mean value. The so-prepared

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beads with average diameter of 1.0±0.05 mm were cured in 0.1M $CaCl_2$ solution with mild stirring at room temperature for 1 h. The resulting beads were gently washed with 100 mL of distilled water followed by 50 mL of physiological solution just before release experiments.

Release of the drug from alginate beads was carried out at 37°C using physiological solution (pH 7.4, ionic strength 0.1M) as a dissolution medium. A stainless steel mesh basket containing 0.25 g of the washed alginate gel beads was connected to a rod. The basket was then immersed in 300 mL dissolution medium set at 37.0±0.5°C and rotated at 100 rpm. At scheduled time intervals, 2 mL of the solution was retrieved and the amount of the drug released was determined by UV detection with wavelength at 257 nm. Swelling property of the beads was studied by a measurement of percentage water uptake as a function of time. 0.250±0.005 g of the beads in a stainless mesh basket was exposed in 300 mL of physiological solution at 37°C under 100 rpm rotation. The mass of the basket dried with a tissue paper was taken at different intervals of time and the average value was calculated. The percentage uptake of water was calculated as

$$\%\ \text{water uptake} = \frac{\text{weight at certain time - initial weight}}{\text{initial weight}} \times 100\%$$

Results and Discussion

Figure 1 shows calcium-alginate gel beads with average diameter of 1.0 mm immobilized with analgetic drug of AB-101. The devices had a perfect spherical shape with regular smooth surfaces suitable for implantation. Degree of immobilization of AB-101 was between 72-75 wt.%. The drug was immobilized as a salt of hydrochloride, so that negative charged alginate macromolecules could interact with positive-dissociated drug. We prepared drug-loaded alginate gel beads on the base of various sodium-alginate with three different M/G ratios, those imply on the difference in time of gel disintegration.

Figure 2 shows release of the drug from the alginate gel beads prepared with three different sodium alginate of various M/G ratio. As shown in the Figure, alginate gels of any kind of M/G ratio release the drug by a S-profile pattern of setting free. In the first stage there is a release of drug following by the Fickian diffusion and corresponding to the square root of time. After a discontinuous time (65 min for A1.8; 80 min for A1.3; and 90 min for A1.0) a quick

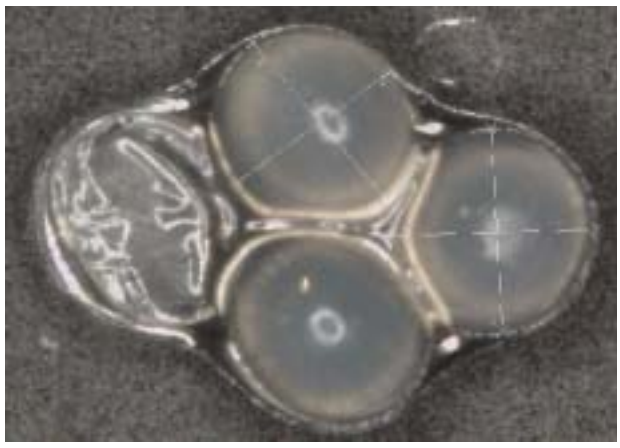

Fig. 1. Photograph of calcium alginate gel beads immobilized with analgetic AB-101. The scale of bar is 1 mm.

release of the drug occurs during short period, which is so-called burst release. During the burst release the remaining drug has been release completely to show a flat kinetics of drug release after all. Time lag of the burst release showed strong dependence on ratio of M/G in the initial alginate matrix. As alginate structure becomes richer with G blocks, the time lag is longer. Increase of G blocks by 80 per cent leads to the enhancement of the time lag by 25-30 min.

Because of the composition of alginate effects on drug release, the behavior of alginate gel must be the whole point of setting drug free. Figure 3 shows the change of weight ratio of the alginate gel beads

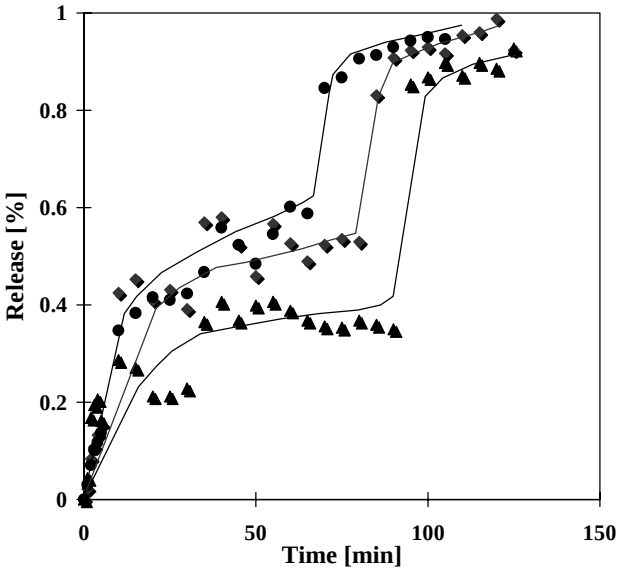

Fig. 2. Release of analgetic AB-101 from alginate gel beads in physiological solution (pH 7.4; 0,1M). Three different M/G ratio alginates are performed as A1.0 (▲), A1.3 (⧫), and A1.8 (•).

of three M/G ratios exposed in the physiological solution containing the sodium ions. In all cases swelling of gels was observed during a first stage, which corresponds to the time lag of burst release. In dependence on M/G ratio the gels swelled 3-5 times up more. If G blocks amount in alginate reduce, expansion of weight increases. After the swelling, gels disintegrated with dissolution in medium. Time of the disintegration was coincided with the burst release of drug. The A1.8 gel collapsed after 70 hs, the A1.3 at 90 h exposition, while A1.0 showed disintegration at 95-100 h.

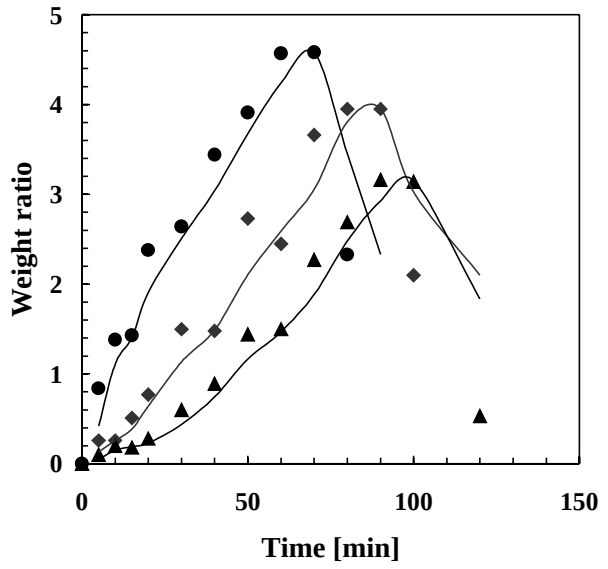

Fig. 3. Kinetics of weight ratio of alginate gel beads exposed in physiological solution (pH 7.4; 0,1M). Three different M/G ratio alginates are performed as A1.0 (▲), A1.3 (♦), and A1.8 (•).

Perhaps the burst release of drug was initiated by disintegration of gel with the following dissolution of polymer in medium. As amount of M blocks increases, the swelling degree of gel enhances too. Obviously, dissociation of M blocks occurs faster than that of G ones due to their dissimilar calcium-gel structure. Previously, Kim et al [7] reported that release from alginate gel beads at pH 6.8 showed nearly zero-order kinetics. The differences in release patterns in our experiments may result from the way of bead preparation. That is, Kim et al. performed release experiments using dry gel beads, while no drying processes for gel preparation were in our experiments. So the alginate gel beads could preserve the microstructure in wet conditions, especially the integrity of surface areas.

Thus, alginate gel beads could be a promising drug delivery device performed as an implant. The use of M/G ratio of alginate might provide a functional time control of drug release, which is important, for instance, for analgetic medicine.

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