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Research Paper

Study of the Use of Alginate Hydrogel Granules in the Encapsulation of Cardiac Drugs

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Abstract

Hydrogels are high-water content materials prepared from cross-linked polymers that are able to provide sustained, local delivery of a variety of therapeutic agents. Use of the natural polymer, sodium alginate, as the scaffold material in hydrogels has been highly pursued thanks to the polymer's biocompatibility, Sodium alginate (SA), which is a naturally occurring non-toxic polysaccharide found in marine brown algae, is one of the polysaccharides employed to fabricat small hydrogel beads, These beads can be prepared using an ionotropic gelation method. In this research Propranolol hydrochloride was used as model drug for loading in calcium alginate beads. Drug encapsulation efficiency (EE) was determined. The swelling ability of propranolol in solutions of different pH value were investigated. They exhibited significant swelling rates when exposed to the slightly alkaline environment. Furthermore, in vitro release of propranolol was investigated. The results suggest that the system has potential to be used as a delivery system for propranolol hydrochloride.

Keyword: Hydrogel; Sodium Alginate; Propranolol- Hydrochloride; Encapsulation; Swelling; Drug Release

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Introduction

Several functions such as blood pressure (BP), heart rate, stroke volume, cardiac output, blood flow of the cardiovascular system is depending on circadian rhythms. Some chronotherapeutic and chronopharmacokinetics have gained the attention of researchers. For instance, capillary resistance and vascular reactivity are higher in the morning and decrease later in the day. Platelet aggregation is increased and fibrinolytic activity is decreased in the morning leading to a state of relative hypercoagulability of the blood [1]. It was postulated that modification of these circadian rhythms triggered by pharmacological agents may lead to the prevention of adverse cardiac events. BP is at its lowest during the sleeping period and rises steeply during the early morning period [2]. The regular BP measurement reading is elevated in most of these patients. If they are elevated, the need for more effective, long-acting antihypertensive therapy is recommended [3]. Pharmacotherapy approach to blood pressure, which targets circadian blood pressure changes increasingly accepted as the important strategy for the treatment. Earlier clinical therapiesare only based on the choice of antihypertensive drugs.

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Incorporating the chronotherapy strategy into routine anti hypertensive strategy was found as major challenging aspect to the clinicians. Propranolol hydrochloride is a nonselective beta adrenergic blocking drug commonly used in the prophylaxis of migraine[4, 5]. It is also used in the treatment of a variety of cardiovascular disorders, such as angina, tachycardia, and hypertension. Due to the short half-life of PPN† (3.9 h) ,PPN has been selected as a drug candidate for developing multiple-unit sustained release dosage forms [6].

Recently the use of biopolymers in the design of hydrogels has received much attention, because of their excellent biocompatibility, biodegradability and environmental sensitivity, etc [7-9].

There is a need to develop an oral drug delivery system that is convenient for patients. Various synthetic and natural polymers like alginate, chitosan and polyesters have been used to develop drug delivery systems for entrapping and delivering drugs orally. Sodium alginate, a salt of alginic acid (brown algae), a linear copolymer of α-guluronic acid and α-mannuronic acid, has the ability to form a gel/meshwork in the presence of divalent cations such as $CaCl_2$. This gel shrinks at acidic pH and erodes at alkaline pH. Therefore, it can be used effectively to deliver drugs to the intestine, which has a pH of >6.7. Moreover, alginate is mucoadhesive and is likely to stick to intestinal mucosa for prolonged periods of time. Various drugs have been effectively delivered orally in alginate beads [10].

Hydrogels are three-dimensional networks composed of hydrophilic polymers, can absorb large amounts of aqueous fluids [11, 12]. Due to their high water content and porosity , hydrogels have drawn much attention in a wide variety of fields such as drug delivery system, tissue engineering, artificial muscles, wound dressing, enzyme biosensor ,contact lens, separation devices, sensors, chemical valves, metal particle preparation, dye adsorption, agriculture (controlled release of fertilizers or pesticides, filters, catalysis, and optically transparent materials) [13, 14]. These gels have the ability to respond to changes in their external environmental conditions like pH [15], temperature [16] and ionic strength [17]. Among these systems pH-responsive hydrogels have been exclusively studied in biomedical field for the controlled drug delivery because this factor can be easily controlled [18].

The hydrophilicity of the network is due to the presence of chemical residues such as hydroxylic (OH), carboxylic (-COOH), amidic (-CONH-), primary amidic ($-CONH_2$), sulphonic ($-SO_3H$), and others that can be found within the polymer backbone or as lateral chains. Nevertheless, it is also possible to produce hydrogels containing a significant portion of hydrophobic polymers, by blending or copolymerizing hydrophilic and hydrophobic polymers [19].

Hydrogels have attracted cosiderable interest for their use in drug delivery due to their unique physical properties [20]. The high porosity that characterizes hydrogels can easily be adjusted by controlling the density of cross-links in their matrix and the affinity to water. Their porous structure also allows drugs to be loaded and then released. The advantages offered by hydrogels for drug delivery applications include the possibility for sustained release, which results in maintaining a high local concentration of an active pharmaceutical ingredient over a long period. The drug can be loaded into a hydrogel and then its release may proceed through several mechanisms: diffusion controlled, swelling controlled, chemically controlled and environmentally responsive release [12]. The aim of the current study was first the investigation of the swelling behavior of calcium alginate beads in different aqueous media. Then, in vitro release properties of the antihypertensive drug propranolol hydrochloride from alginate beads were studied.

Materials and Methods

Materials

Sodium alginate and propranolol hydrocholoride were obtained from Sigma (USA). Calcium chloride was purchased from Merck. All reagents were at least analytical grade, and were used as received.

Preparation of calcium alginate Beads

1.3% calcium solution (w/v) and 1.0% alginate solution (w/v) were prepared by dissolving 1.3 g of calcium chloride dihydrate and 1.0 g of sodium alginate in 100 mL of deionized water. The calciumalginate beads were prepared by dropping 10 mL alginate solution into a gently stirred 30 mL $CaCl_2$ solution for 15 min. The wet calcium-alginate beads remained for 15 min under gentle magnetic stirring in the media, and then the formed calcium alginate beads were collected and rinsed with deionized water and dried in air overnight.

Preparation of Propranolol-HCl Loaded Hydrogel Beads

Twenty-five milligrams of propranolol was dispersed in 10 mL solution containing 1% sodium alginate, and then the other processes were the same as the preparation of the mixed beads.

† .propranolol hydrochloride

Swelling Studies

Swelling characteristics of the beads were determined by immersing dried test beads in two aqueous media: simulated gastric fluid (SGF, pH 1.5), and simulated intestinal fluid (SIF, pH 6.8). Accurately weighed amounts of beads were immersed in 40 mL media solution and the beads were removed from the swelling medium at specific time intervals. They were blotted with filter paper to absorb water on the surface and then weighed immediately. Swelling ratio (SR) of the sample was calculated according to the following expression:

$$SR\ \% = [\ (W-W_0)\ /\ W_0\ )] \times 100 \qquad (1)$$

where W is the weight of the swollen beads and W_0 is the initial weight of the beads.

Calibration Curves

Stock solutions of propranolol hydrochloride were prepared by dissolving propranolol in pure water at a specific concentration. Propranolol stock solution was further diluted with pure water to obtain the different working solutions.

Propranolol encapsulation efficiency

The encapsulation efficiency was determined indirectly. The amount of propranolol loaded in beads was calculated by difference between the total amounts of propranolol in injected droplet and the amount of propranolol that diffused in $CaCl_2$ solution.

$$\text{Encapsulation efficiency (\%)} = \frac{proporanolol\ initial\ ammount - free\ propranolol\ amount}{total\ amount\ of\ propranolol} \qquad (2)$$

Propranolol concentration was determined spectrophotometrically (Rayleigh, UV-1601-made in china) using absorbance measured at 289 nm.

In vitro Release study

Dried beads were placed in phosphate buffer pH = 6.8 (2h/120 rpm) at 37°C. At predetermined time intervals 2 ml solution was withdrawn and assayed spectrophotometrically at 289 nm. The percentage of cumulative amount of released propranolol was determined from calibration curves and the released amount of propranolol-HCl from the beads was determined using Eq.(3)

$$\text{Drug release (\%)} = [R_t/L] \times 100 \qquad (3)$$

where L and Rt represent the initial amount of drug loaded and cumulative amount of drug released at time t.

Results and discussion

Swelling characteristics

Figure 1 shows the swelling behavior of alginate hydrogels. As shown in the Figure, the test beads exhibited significant swelling rates when exposed to the slightly alkaline environment.

The hydrogel beads show a high swelling in simulated intestinal fluid at pH 6.8 and have a very lower swelling in simulated gastric fluid (SGF) at pH=1.5. The swelling behavior of the beads is mainly attributed to the hydration of the hydrophilic groups of alginate.

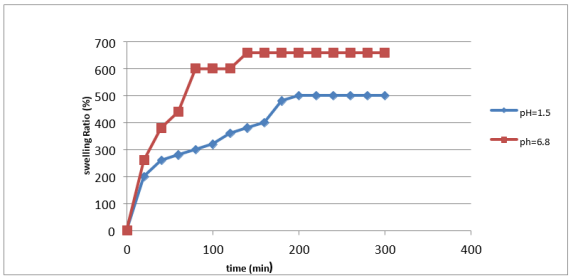

Figure1. Swelling characteristics of dry beads in SGF (pH 1.5), and SIF (pH 6.8)

Drug release behavior

The encapsulation efficiency of Propranolol in calcium–alginate beads were found to be 66% (Figure 2). The propranolol release behavior from beads was studied in SIF (at pH=6.8). The drug release from the alginate beads depends on the penetration of the dissolution medium into the beads, swelling and dissolution of alginate matrix, and the dissolution of the drug subsequent to leaching through the swollen matrix. The release profiles of propranolol-HCL from the prepared beads are presented in Figure 2.

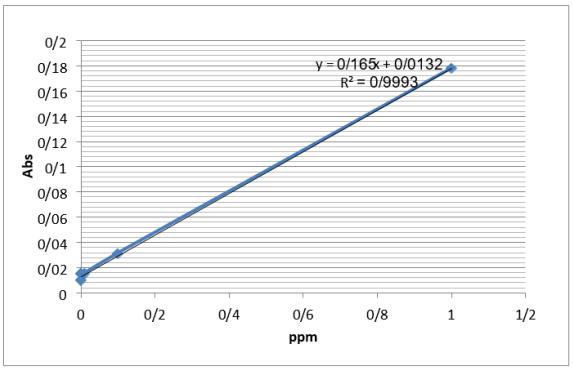

Figure 2. Calibration curve for propranolol hydrochloride

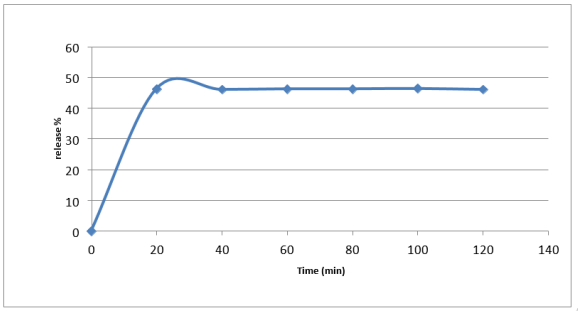

Figure 3. Propranolol release profile at SIF (phosphate buffer, pH 6.8)

Conclusion

The main objective of this study was to prepare spherical propranolol – loaded alginate from high viscous alginate solutions**.** this study shows that the swelling characteristics and release properties of propranolol from calcium alginate beads. The overall results demonstrate that calcium alginate can deliver drugs to the intestinal tract and keep the drug release slowly and persistently. Therefore, it can thus be employed as a promising vehicle for oral drug delivery in the intestinal tract and reduce the side-effects of propranolol.

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