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Preparation and characterization of pH-sensitive alginate-g-poly(*N*-vinyl-2-pyrrolidone)/gelatin blend beads

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ABSTRACT

In this study, pH-sensitive alginate-g-poly(*N*-vinyl-2-pyrrolidone)/gelatin (SA-g-PVP/Gel) blend beads were produced as controlled release system. Structural features of the SA-g-PVP/Gel beads were characterized by FTIR, X-RD, DSC, SEM and mercury intrusion-porosimetry. *In vitro* nifedipine (NFD) release was investigated at pH 1.2 for 2 h and followed by immersing at pH 7.4 for 6 h. Effects of diverse parameters such as grafting of PVP, copolymer/gelatin blend ratio, concentration of cross-linker and drug amount on the release of NFD were investigated. The NFD release from SA-g-PVP/Gel beads demonstrated pH-sensitivity of drug release. Cytotoxicity experiments of SA-g-PVP and SA-g-PVP/Gel beads displayed their biocompatible character.

Introduction

Controlled release formulations such as micro/nano-spheres, pellets, and beads have several advantages compared to conventional formulations. These advantages are: minimized drug dose, extended drug administration range and improved life quality of patient by protecting the drug side effects [1,2]. In these systems, the drug release rate is controlled by the balance between swelling of polymeric network and the drug diffusion [1]. Many controlled drug delivery systems have been developed by using various natural or synthetic polymeric hydrogels [3–6]. Hydrogels are three-dimensional network structures, which are synthesized by crosslinking of polymers. They can absorb water up to thousands folds of their dry weight [4]. Hydrogels are also used in industrial field including cell encapsulation, enzyme immobilization, and various biomedical applications [5,7–10]. Generally, natural polymeric hydrogels are preferred to synthetic hydrogels due to low cost, biocompatibility, and biodegradability [6]. However, there are also some synthetic polymeric hydrogels that are used as a carrier in controlled release systems due to their biological compatibility. Hence, natural polymer hydrogels can be modified with synthetic polymers. Grafting of synthetic polymer onto natural polymer is one of the simplest techniques to modify of natural polymers. When adding the synthetic polymer into the natural polymer chains, the chemical, physical, mechanical and thermal properties of the resultant graft copolymer will be improved compared to the natural polymers [6,11]. Modified natural polymers are used in many applications, such as: controlled drug release, heavy metal or dye adsorption, enzyme immobilization, cell encapsulation, and gene carrier [12–17].

Alginate is a biocompatible, biodegradable and non-toxic natural polysaccharide, which can be produced from all species of brown algae [18]. It contains two main components α-L-guluronic acid (G) and β-D-mannuronic acid (M) [18,19]. Alginate and alginate derivatives have been used in pharmaceutical industry and food industry as a gelling agent, a colloidal stabilizer, and a thickening agent [20]. The sodium alginate, which can be cross-linked with multivalent cations or glutaraldehyde, is used as a drug release matrix in pharmaceutical applications [21].

The hydrogels of sodium alginate, which are cross-linked by calcium ions, are limited to use due to problems of stability in high-level pH media. Furthermore, the calcium alginate hydrogels are generally very permeable. This permeability limits the application of hydrogels especially in the release of water-soluble drugs. These disadvantages can be prevented by blending alginate with other polymers such as chitosan [22,23], gelatin [20], hydroxypropyl-methylcellulose [24], and methylcellulose [21]. On the other hand, glutaraldehyde is used to cross-link sodium alginate prolonging drug release and increasing the durability of hydrogels [5,19].

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Gelatin is a natural, biodegradable, and biocompatible protein obtained by hydrolysis of collagen [25]. It is a heterogeneous protein structure located within 18 amino acids [25,26]. Gelatin, which used in cosmetics, pharmaceuticals as well as food products for a long time, is approved as safe polymer by the United States Food and Drug Administration (US FDA) [27]. Due to these important characteristics, gelatin it is used in numerous applications in the various fields such as drug and growth factor release and tissue engineering [28–32].

Hypertension is one of the most important risks associated with heart diseases. Nifedipine (NFD) is extensively used in the treatment of angina, hypertension, and myocardial infarction as a calcium channel antagonist [33–35]. NFD is weakly water-soluble drug and *in vivo* plasma half-life is 2 h [34,35]. Therefore, NFD fast-release dosage forms require to be administered two to three times per day [33–35]. Using this therapeutic dose induces significant changes in plasma drug concentration; this might induce intense toxicity and side effects in susceptible individuals [33,36]. Recently, NFD has been used as controlled release dosage forms [1,21,37].

In our previous study [6], controlled release of indomethacin from alginate-graft-poly(*N*-vinyl-2-pyrrolidone) beads under *in vitro* conditions was investigated. The release of indomethacin was found to be quite low (in the range of 30–77%) [6]. In this study, gelatin was blended with the SA-g-PVP in order to increase the release of NFD, which is a poorly water-soluble drug. By using gelatin, hydrogel beads can be more swelling in acidic pH. As a result, the release of basic drugs such as NFD could be increased in the stomach [38].

In the present study, SA-g-PVP/Gel hydrogel beads containing NFD was produced *via* gelation method. Although many studies with similar concepts were reported in the literature, the combination of SA-g-PVP/gelatin was not studied before. The objective of the work is to investigate the effects of gelatin on the drug release profile of PVP grafted alginate beads as well as its swelling properties to achieve optimized SA-g-PVP/Gel blend beads for potential applications in load-bearing drug delivery carriers. SA-g-PVP/Gel/NFD solution was cross-linked by glutaraldeyde (GA). The obtained blend beads were characterized with Fourier transform infrared (FTIR), differential scanning calorimetry (DSC), X-Ray diffraction (X-RD), and scanning electron microscope (SEM) studies. Moreover, particle diameter, bead production yield, entrapment efficiency, and pore size of the obtained beads were determined. Swelling ratio and NFD release of the beads were carried out at pH 1.2 (0.1 N HCl) and pH 7.4 phosphate buffer solution. The effect of factors such as, the PVP grafting percentage, SA-g-PVP/gelatin blend ratio, concentration of GA, and drug amount on the release of NFD was investigated.

Materials and methods

Materials

Sodium alginate, gelatin, nifedipine, ethanol, acetone, and methanol were supplied from Sigma Chemical Co. (Louis, USA). *N*-vinyl-2-pyrrolidone and hydrochloric acid were purchased from Fluka Chemie AG (Buchs, Switzerland). Azobisisobutyronitrile, sodium dodecyl sulphate (SDS), and other reagents were obtained from Merck (Darmstadt, Germany).

Preparation of SA-g-PVP/Gel beads

SA-g-PVP copolymers were synthesized as reported in our previous study [6]. Various copolymers were synthesized by changing the concentration of monomer. The grafting yield results were presented in Table 1.

All the hydrogel beads were prepared according to gelation method. Briefly, SA-g-PVP and gelatin solutions with different blend ratio containing NFD were mixed and stirred to get a well-dispersed suspension for 24 h. The polymer mixture was transferred drop wise into GA/HCl solution using a peristaltic pump (Masterflex, L/S Digital Economy Drive, USA). The SA-g-PVP/Gel beads were then taken out from the GA solution after 15 min, and washed with water four times to remove the excess GA/HCl. The blend beads were dried entirely in vacuum oven at 35 °C. The formulation parameters and codes of beads are summarized in Table 1. Empty blend beads were formed similarly without NFD to determine swelling behavior. Scheme 1 displays the schematic illustration of SA-g-PVP/Gel blend bead preparation and pH-dependent drug release from SA-g-PVP/Gel beads in aqueous solution. Twelve samples from various bead types were chosen in order to measure the diameter of beads, and their diameters were determined by using a digital caliper (Mitutoyo IP.65, Japan).

The yields of the blend beads for different designs were determined as follows:

$$Yield(\%) = \frac{Mass\ of\ total\ obtained\ bead}{(Mass\ of\ polymers + Mass\ of\ added\ NFD)} \times 100 \qquad (1)$$

Table 1
Formulation parameters of the hydrogel beads.

Code	Polymer	Copolymer/gelatin ratio	Grafting yield of copolymer (%)	Concentration of GA% +10 N HCl% (v/v)	Exposure time to GA (min)	Amount of NFD% (w/w)
G_1	SA-g-PVP_1	–	12.21 ± 0.39	0.5+2	15	10
G_2	SA-g-PVP_2	–	15.09 ± 0.34	0.5+2	15	10
G_3	SA-g-PVP_3	–	19.88 ± 0.23	0.5+2	15	10
C_1	SA-g-PVP_1/Gel	90/10	12.21 ± 0.39	0.5+2	15	10
C_2	SA-g-PVP_1/Gel	85/15	12.21 ± 0.39	0.5+2	15	10
C_3	SA-g-PVP_1/Gel	60/40	12.21 ± 0.39	0.5+2	15	10
D_1	SA-g-PVP_1/Gel	85/15	12.21 ± 0.39	0.25+1	15	10
D_2	SA-g-PVP_1/Gel	85/15	12.21 ± 0.39	0.75+3	15	10
D_3	SA-g-PVP_1/Gel	85/15	12.21 ± 0.39	0.5+2	15	20
D_4	SA-g-PVP_1/Gel	85/15	12.21 ± 0.39	0.5+2	15	50

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