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Short communication

Impact of gelation period on modified locust bean-alginate interpenetrating beads for oral glipizide delivery

Paramita Dey[a,*], Biswanath Sa[a], Sabyasachi Maiti[b]

[a] Department of Pharmaceutical Technology, Jadavpur University, Kolkata 700032, India
[b] Department of Pharmaceutics, Gupta College of Technological Sciences, Ashram More, G.T. Road, Asansol 713301, West Bengal, India

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ABSTRACT

In this work, the effect of hydrogelation period in the design of glipizide-loaded biopolymer-based interpenetrating network (IPN) beads was investigated. Carboxymethyl locust bean gum and sodium alginate IPN beads were prepared by ionic crosslinking method using aqueous aluminium chloride salt solution as gelation medium. The longer exposure of the IPN beads in the gelation medium caused a considerable loss of the drug (~8%), and also affected their surface morphology and drug release performance. Spherical shape of the IPN beads was observed under scanning electron microscope (SEM). The diameter of IPN beads increased with increasing gelation time. The IPNs cured for 0.5 h exhibited slower drug release kinetics in HCl (pH 1.2) and phosphate buffer (pH 7.4) solution than those incubated for 1–2 h. The drug release occurred at a faster rate in phosphate buffer solution and continued for a minimum period of 8 h. The IPNs cured for the lowest period obeyed polymer chain-relaxation phenomenon as dominating mechanism for drug release. However, all the IPNs followed anomalous mechanism of drug transport. The drug release corroborated well with pH-dependent swelling behaviors of the IPNs. Thus, IPN beads cured for 0.5 h were found most suitable for controlled delivery of BCS class II anti-diabetic drug glipizide.

1. Introduction

Naturally occurring carbohydrate polymers are gaining popularity day by day in the design of pharmaceutical dosage forms, especially due to their low cost, easy amenability of chemical modification, biodegradability and biocompatibility [1]. Moreover, they can form cross-linked three-dimensional hydrogel network that can swell in biological fluids without dissolving [2,3]. This property of hydrogel can help in achieving extended drug release profiles in simulated biological fluids. Hydrophilic natural polymers such as alginate, gellan gum, guar gum, locust bean gum have a long history of forming metal ion induced hydrogel beads either in their native or carboxymethyl derivative forms. Sometimes, a single biopolymer hydrogels becomes insufficient to meet the demand in terms of physicochemical properties and extended drug release performance. Recently the concept of interpenetrating network (IPN) opens up the doors to develop novel multi-particulate drug delivery systems. IPN is a composite of two or more polymers where at least one polymer network is synthesized or crosslinked independently in the immediate presence of the other [4].

The IPNs of natural polymers such as guar gum [5], gellan gum [6], xanthan gum [7] in conjunction with synthetic poly(vinyl alcohol) have been proposed in order to have a control over drug release. However, the application of two carbohydrate polymers in the design of IPN is least studied and thus, could be interesting in optimizing drug delivery. In our earlier reports [8,9], we characterized IPNs of sodium alginate and carboxymethyl locust bean gum in terms of various physicochemical and pharmacodynamic properties. Since we have developed IPN in an environmentally benign ionotropic gelation technique, the role of hydro-gelation period on the properties of IPNs must be fully disclosed. Thus, the purpose of this communication was to provide an understanding of the effect of gelation period on the properties and controlled drug release performance of the IPNs.

The clinical significance of this study can be easily explained by highlighting a report that the worldwide estimate of diabetic cases among adults (>20 years) was about 171 million in the year 2000 and will rise to 366 million by 2030 [10]. Under such circumstances, an initiative to the development of novel controlled release anti-diabetic formulations could gain an appreciation in terms of the reduction or avoidance of dose-related side effects of the drugs.

* Corresponding author. Tel.: +91 9051477424.
E-mail address: paramita.dey6@gmail.com (P. Dey).

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Glipizide is an oral blood glucose lowering drug and has a short elimination half life (2–4 h) in normal subjects. Hence, controlled release biopolymer-based IPN formulation could be advantageous for oral delivery of glipizide.

2. Materials and methods

2.1. Materials

Sodium alginate (240 kDa) was obtained from SD Fine Chem Pvt. Ltd., Mumbai, India. Sodium carboxymethyl locust bean gum having degree of *O*-carboxymethyl substitution of 0.68 ± 0.09 was synthesized from locust bean gum (HiMedia Laboratories Pvt. Ltd., Mumbai, India) in our research laboratory. Glipizide was received as gift from Micro Labs Ltd., Hyderabad, India. Aluminium chloride ($AlCl_3$, $6H_2O$) was purchased from Loba Chemie Pvt. Ltd., Mumbai, India and rest of the chemicals was of analytical grade.

2.2. Preparation of IPN beads

Ten milliliters of 4% (w/v) aqueous polymeric blend of modified locust bean gum and sodium alginate (3:1) was dropped into 100 ml of 5% (w/v) aluminium chloride solution *via* 18G flat-tip needle. The droplets were cured for different periods: 30, 60 and 120 min and the hydrogel beads formed thereafter were collected by filtration. The beads were washed with distilled water (3× 50 ml) to remove gelation medium adhered to the bead surface and air-dried. The composition of IPN bead formulation was given in Table 1.

2.3. Scanning electron microscopy

The dried bead samples were gold-coated to examine their surface topography under scanning electron microscope (JEOL JSM 6360, Japan). The images were taken at an acceleration voltage of 15 kV at required magnification with a secondary electron image as a detector.

2.4. Diameter of beads

The bead diameter was measured by a digital caliper (99MAD014 M, Mitutoyo, Tokyo, Japan) with an accuracy of 0.001 mm. Fifty particles were measured randomly for each formulation and the mean diameter was reported with standard deviation.

2.5. Drug entrapment efficiency

The actual amount of drug present in a known amount of dried IPN beads (10 mg) was assessed spectrophotometrically (UV1, Thermo Spectronic, UK) at 276 nm. The sample for analysis was prepared as follows. To extract the drug completely, the bead samples were crushed and digested in phosphate buffer solution (pH 7.4) for 24 h. The sample suspension was filtered through Whatman Filter paper (No. 1) and the filtrate was assayed. Finally, the dug entrapment efficiency (DEE) was calculated by the following equation:

$$\mathrm{DEE}(\%) = \frac{\text{amount of drug estimated in known sample}}{\text{theoretical amount of drug in same sample}} \times 100$$

2.6. Drug release study

In vitro drug release study was conducted in enzyme-free, simulated gastric (HCl, pH 1.2) and intestinal (phosphate buffer, pH 7.4) fluids. Accurately weighed 50 mg of IPN samples were placed at the bottom of the dissolution vessel and then 900 ml of each simulated fluid were added. The paddle of the apparatus (VDA-6D, Veego Instrument Corporation, Mumbai, India) was set at 50 rpm. The experiment was carried out at a temperature of 37 °C. The percentage drug release was monitored by withdrawing and subsequently analyzing 5 ml of the samples at different times at 276 nm in UV-vis spectrophotometer. The same volume of fresh buffer solution was immediately replaced at each time points. Each formulation was tested in triplicate.

2.7. Swelling experiment

Gravimetric method was followed for measuring degree of swelling of the IPN beads. Ten milligrams of dry IPN beads were immersed into 50 ml of enzyme-free simulated fluids. The beads imbibed the fluid and the weight of swollen beads (Metler Toledo, AB 204-S, Switzerland) was recorded time to time. As a precautionary measure, the wet beads were blotted with tissue paper to avoid excessive weight of the particles. The degree of swelling was measured by the equation given below.

$$\text{Swelling degree} = \frac{(\text{weight of beads at time } t - \text{weight of dry beads})}{(\text{weight of dry beads})}$$

2.8. Statistical analysis

The drug entrapment efficiency values and single point dissolution data of the IPN beads were fitted into statistical software (GraphPad Prism, Version 3.00, Trial) for evaluating any significant differences (one-way ANOVA) that might have occurred as a function of gelation period at $\alpha = 0.05$. An indication of significant difference was considered when $p < 0.05$.

3. Results and discussion

In this communication, the effect of exposure time of the nascent IPN beads to ionic cross-linking medium was evaluated especially with reference to their drug entrapment efficiency, morphology and size, swelling and drug release characteristics. In order to do so, the mass ratio of modified locust bean gum and sodium alginate in the design of IPN beads was kept constant (3:1). The possible reason can be explained as follows. Since both the polymers are polysaccharides, they possessed variable number of hydrophilic hydroxyl and carboxyl groups in their chemical structure. Therefore, any variation in the molar ratio of the polymers could affect the swelling behaviors and consequently the drug release characteristics of IPN beads. Kim et al. [11] demonstrated that the swelling ratio increased with increasing molar ratio of chitosan in chitosan-poly(vinyl alcohol) IPNs due to greater hydrophilicity of chitosan than poly(vinyl alcohol).

Scanning electron microscopic features of the IPNs were demonstrated in Fig. 1. The beads were almost spherical in shape regardless of the gelation period (Fig. 1a and b). The surface of IPN1 beads was free of any pores (Fig. 1c); however the pores were visible over the surface of IPN3 beads (Fig. 1d). This observation was also true for IPN2 beads. The pores could be formed due to continuous leaching of drug during excessive curing in gelation medium. Mi et al. [12] reported that highly crosslinked chitosan beads may form porous structures leading to easily crackable brittle structure.

The diameter of the IPN beads gradually increased from 1245 μm to 1568 μm with the increase in gelation period from 0.5 h to 2 h (Table 2). As the polymer sol droplets contacted highly concentrated aluminium chloride solution, the droplets were found