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Effect of different cross-linking methods and processing parameters on drug release from hydrogel beads

Shataneek Mitra, Siddhartha Maity, Biswanath Sa*

Division of Pharmaceutics, Department of Pharmaceutical Technology, Jadavpur University, 188, Raja S.C. Mallik Road, Jadavpur, Kolkata 700032, West Bengal, India

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ABSTRACT

The purpose of this work was to evaluate different methods of cross-linking for developing diltiazem–resin complex loaded carboxymethyl xanthan gum (CMXG) hydrogel beads to achieve highest possible drug entrapment and extended release for effective cardio-protection. The hydrogel beads were prepared by ionic cross-linking and dual cross-linking using simultaneous (SIM) and sequential (SEQ) methods. Among the three methods, SEQ method produced smaller sized beads having higher drug entrapment efficacy and prolonged release characteristics as evidenced from mean dissolution time and diffusion coefficient of drug. Keeping the concentration of ionic cross-linker constant, increase in the amount of covalent cross-linker and cross-linking time decreased the drug release. Higher release of the drug in acid solution was attributed to the higher solubility of the basic drug and higher swelling of the matrices in acid solution. Comparison of FTIR spectra, drug content and dissolution profiles indicated that the drug was stable in the beads when kept under stress condition up to 3 months. In conclusion, the sequential method was found superior for producing CMXG hydrogel beads as a prolonged release delivery device in cardiovascular diseases.

1. Introduction

Cardiovascular diseases (CVD) have become a dominant cause of morbidity and mortality in most countries. Clinical manifestations of CVD include angina pectoris, ischemia, hypertension, arrhythmia, heart failure and sudden death. While in 2008 worldwide approximately 40% adults aged 25 years and above had been diagnosed with hypertension [1], about 3.2% had been detected to suffer from angina pectoris [2]. In addition to life-style modification, pharmacotherapy with antihypertensive and anti-anginal agents is required to reduce symptom and events of CVD.

Diltiazem–HCl, a calcium channel blocker is a popular and effective drug for adequate control of hypertension [3] and angina pectoris [4]. However, because of short half-life of 3.5 h, the drug is administered three to four times a day [5]. To avoid multiple dosing and provide better therapeutic management, sustained release therapy appears to be more rational [6]. Moreover, patients are frequently converted from immediate release to sustained release diltiazem formulation for the treatment of symptomatic CVD [7].

Multi-unit sustained release dosage form such as microcapsules, microspheres, microbeads offer several advantages over single unit sustained release tablets [8]. Recently, development of natural polymer based microbeads has been a focused research area as the polymers are available from natural source, non-toxic, and biocompatible [9] and can be processed under all aqueous eco-friendly condition [10].

Development of microbeads using natural polymers especially polysaccharide involves either ionic cross-linking of di- or trivalent metal ions with the carboxyl function already existing or introduced by carboxymethylation in favorable position of the polysaccharide backbone [11,12] or chemical cross-linking of glutaraldehyde, polyethyleneimine with hydroxyl group of the polymer devoid of carboxyl groups [13,14]. Yet another development of microbead involves dual cross-linking with ionic and chemical cross-linking agents [15]. One of the major disadvantages of formulation of hydrogel beads of water soluble drugs is low drug entrapment efficiency which may be avoided by tagging the drugs with suitable ion exchange resin. Diltiazem HCl, a cationic drug having fairly high aqueous solubility (565 mg/ml) [16] has been used in this study.

This work was envisaged to develop diltiazem–cation exchange resin loaded carboxymethyl xanthan gum hydrogel beads by three methods viz, ionic cross-linking with $AlCl_3$, simultaneous

* Corresponding author. Tel.: +91 9748091005.
E-mail address: biswanathsa2003@yahoo.com (B. Sa).

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cross-linking with $AlCl_3$ and glutaraldehyde (GA), and sequential cross-linking involving GA treatment of ionically preformed hydrogel beads, and to evaluate the beads with respect to especially drug entrapment efficiency, and release characteristics. The effect of other formulation parameters on the sustained drug release characteristics of the beads prepared by the most suitable method was also explored.

2. Materials and methods

2.1. Materials

Diltiazem Hydrochloride (DTZ) (Indian Pharmacopoeia) was obtained as gift sample from Dr. Reddy's Laboratories Ltd, Hyderabad, India. Indion-254 (sulphonic acid cation exchange resin in Na^+ form) was purchased from Ion Exchange Pvt. Ltd., Mumbai, India. Xanthan gum (XG), monochloro acetic acid (MCA), aluminum chloride hexahydrate ($AlCl_3$) and glutaraldehyde (GA) were purchased from SD Fine-Chem. Pvt. Ltd, Mumbai, India. De-mineralized (DM) water was used throughout the study.

2.2. Preparation of drug-resin complex (Resinate)

DM water and methanol washed resin was activated by treating thrice alternately with 1 (M) NaOH (60 ml) and 1 (M) HCl (60 ml), and washing after each treatment with DM water. Finally, the resin in hydrogen/acid form was washed repeatedly with DM water till the elute was neutral to litmus, vacuum dried at 50 °C to constant weight, and fractioned by sieving. Accurately weighed amount of the fraction retained on No. 350 BS screen was added in 75 ml DM water containing 0.80 mg/ml of DTZ and stirred for 3 h at 30 °C. The resulting drug-resin complex was vacuum filtered, washed repeatedly with DM water till the drug concentration in the filtrate become negligible (as evident by negligible absorbance in UV-spectrophotometer at 236 nm), and dried in vacuum at 50 °C to constant weight.

2.3. Preparation of resinate-loaded hydrogel beads

Three different approaches, namely ionic cross-linking (IC), dual cross-linking either by simultaneous (SIM) or sequential (SEQ) method were used to prepare resinate-loaded hydrogel beads. Required amount of resinate (20% w/w of polymer) was homogenously dispersed in a 2.5% w/v solution of CMXG in DM water, and extruded through a 21 G flat-tip hypodermic needle in various cross-linking solution. Following cross-linking for various time periods, the gelled beads were removed by filtration, washed repeatedly with DM water and dried at 45 °C to constant weight. In IC method, the extruded beads were treated for 15 min with 50 ml of 2.5% w/v $AlCl_3$ solution. In SIM method, the beads were cross-linked in a mixture of 50 ml of 2.5% w/v $AlCl_3$ and 5% v/v GA solution for 15 min. In SEQ method, the hydrogel beads were first prepared by IC method, and then the dried hydrogel beads were further cross-linked with 50 ml of 5% v/v of GA solution for 15 min. Further, the beads prepared by SEQ method were treated with different concentration of GA solution (0.5 to 5% v/v) for different cross-linking time (5 to 30 min). The composition of the various resinate-loaded hydrogel beads are shown in Table 1. Drug free resin-loaded hydrogel beads were prepared in the similar way and the composition is shown in Table 2.

2.4. Measurement of the size of hydrogel beads

The diameter of the resinate-loaded hydrogel beads was measured using a Digimatic Caliper (CD-6″CS, Mitutoyo, Japan) having an accuracy of 0.01 mm. The average diameter of the 50 particles per batch was calculated.

2.5. Scanning electron microscopic (SEM) study

Resinate-loaded beads were mounted onto stubs using double-sided adhesive tape and sputter coated with gold using a sputter coater (S150, Edward, UK). The coated beads were observed under Scanning electron microscope (JSM-5200, Jeol, Japan) at low and high magnifications. The acceleration voltage used was 10 kV.

2.6. Drug entrapment efficiency (DEE)

About 50 mg of resinate-loaded hydrogel beads, accurately weighed, were immersed in 250 ml buffer solution of pH 6.8 and was kept for 24 h with continuous shaking. The beads were finally crushed and shaken for another 1 h. Then the solution was filtered and an aliquot, following suitable dilution, was analyzed at 236 nm using a spectrophotometer (UV-2450, Shimadzu, Japan). The actual amount of DTZ present in the hydrogel beads was calculated using a calibration curve constructed in buffer solution of pH 6.8. Drug entrapment efficiency was calculated by using the following relationship:

$$\text{DEE} = \left(\frac{\text{actual amount of drug present}}{\text{theoretical amount of drug loaded}}\right) \times 100$$

2.7. In-vitro drug release study

In-vitro dissolution study was carried out in acid solution of pH 1.2 and buffer solution of pH 6.8 using a USP-II dissolution rate test apparatus (TDP-06P Electro Lab, Mumbai, India). About 50 mg of resinate-loaded hydrogel beads, accurately weighed, were placed in 500 ml acid solution of pH 1.2 or 500 ml buffer solution of pH 6.8 at 37 ± 0.5 °C and rotated with paddle at 75 rpm. At different time interval, aliquot was withdrawn and replenished immediately with the same volume of fresh respective medium maintained at 37 ± 0.5 °C. Undiluted or suitably diluted withdrawn samples were analyzed spectrophotometrically at 236 nm. The cumulative percentage of drug released at each time point in acid solution of pH 1.2 and buffer solution of pH 6.8 were calculated from the calibration curves constructed in the respective medium. Considering the transit time and pH values encountered in the gastrointestinal tract, dynamic in-vitro drug release from the beads prepared by SEQ method was conducted by replacing the acid solution of pH 1.2 after 2 h with buffer solution of pH 6.8.

2.8. Swelling study

About 50 mg of drug free resin-loaded hydrogel beads were immersed separately in 50 ml acid solution of pH 1.2 and buffer solution of pH 6.8 at 37 °C. The hydrated beads were withdrawn from the respective medium at different time points, blotted carefully to remove excess surface water from the swollen beads, and weighed. The percentage swelling of the hydrogel beads was calculated by using the following formula:

$$\text{Percentage swelling} = \left(\frac{(W_w - W_i)}{W_i}\right) \times 100$$

where W_i = initial weight of dry beads at time 0, W_w = weight of swollen beads at time t after immersion in the respective test medium.