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Research paper

Tailored-interpenetrating polymer network beads of κ-carrageenan and sodium carboxymethyl cellulose for controlled drug delivery

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ABSTRACT

Interpenetrating polymer network (IPN) beads of κ-Carrageenan and sodium carboxymethyl cellulose (SCMC) containing Ibuprofen were prepared by water-in-water emulsion gelation process using $AlCl_3$ as a cross-linking agent. The impact of different formulation variables like polymer ratio, gelation time, concentration of crosslinker on physico-chemical parameters and in-vitro drug release were studied. The IPN beads were investigated through Scanning electron microscopy (SEM), Fourier transform infrared (FTIR) spectroscopy, X-ray diffraction (XRD) and differential scanning calorimetry (DSC) analysis. The prepared beads were slightly rough, folded spherical in shape and reflected improved drug encapsulation efficiency. Swelling ability and drug release of beads in alkaline medium was substantial as that of acidic medium. Formulations showed non-Fickian transport mechanism. The results of the study indicate that drug-loaded pH sensitive IPN beads could be used to diminish drug release in an acidic medium and to regulate the drug release in alkaline medium, which would help to minimize the gastric side effects of the model NSAID ibuprofen.

1. Introduction

Interpenetrating polymer network (IPN) is an ingenious drug delivery system, with several advantages like high swelling capacity and tremendous mechanical strength which plays a significant function in the targeted and controlled drug delivery. IPN has emerged as a trending scaffold to carry the drug within its minuscule spherical body and target into the specific part of the body, in the present investigation it is gastrointestinal tract. The modified polymers have the capability to sense the pH of the gastrointestinal tract and release the drug at the desired site of action. These progressive properties of IPNs have attracted considerable attention in pharmaceutical field, especially in the area of novel drug delivery systems. By developing IPN system one has the opportunity of developing materials with a range of properties that will conquer the disadvantages of conventional system of the individual polymer network. These IPN's are basically hydrogels with three dimensional hydrophilic polymer networks that are capable of absorbing large amounts of water [1]. Due to their several advantages like hydrophilicity, biocompatibility and lack of toxicity they have demonstrated excellent performance in controlled delivery of active molecules [2]. One of the most outstanding accomplishments of hydrogels in drug delivery is the development of stimuli-sensitive delivery systems which shows sudden and gradual change of swelling properties in response to stimuli (like temperature, pH, ionic strength, light, electric and magnetic field etc.). Because of these stimuli sensitive behavior, hydrogels can be employed to render the active molecule to the desired target site [1].

Previously many pharmaceutical scientists have extensively investigated on the synthesis of IPN based on natural polymers for controlled or targeted drug delivery. Among the most abundant natural polymers, polysaccharides (alginic acid, chitosan, gellan gum, locust bean gum, xanthan gum, carrageenan, etc.) have been studied in absolute feature in preparing gastro-protective IPN beads to protect the gastric mucosa from the irritant action of drug [3–6]. Hezaveh et al. have also synthesized kappa-carrageenan/carboxymethyl cellulose IPN beads with genipin as cross linking agent in order to modify the drug release mechanism of beta carotene [7].

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Carrageenan (CG) is naturally occurring high molecular polysaccharide extracted from red seaweeds. There are three main types of CG depending on the number and position of easter sulfate groups; kappa (κ), iota (i), and lambda (λ) carrageenan. κ-CG comprise of repeating units of (1,3)-D-galactopyranose and (1,4)-3, 6-anhidro-α-D-galactopyranose with sulfate groups in a certain position with certain amount [8]. κ-CG has ability to form thermoreversible gel and because of their gelling, viscosity enhancing, and proven safety properties [9], biocompatibility and biodegradability, it is widely used in food and non-food industry and also in pharmaceuticals [10].

The purpose of the present study is to develop pH sensitive IPN beads of κ-CG and sodium carboxymethyl cellulose (SCMC) using $AlCl_3$ as a crosslinking agent and to evaluate the beads for encapsulation efficiency, swelling behavior and release of a model drug from the prepared beads. High ionization tendency of CG (because of the presence of hydrophilic sulfate groups) and less sensitivity to salt solution was our foremost design for developing these κ-CG and SCMC based IPN beads. It is expected that the swelling and drug release of these beads would be minimized in the gastric area however as the beads pass down the GIT, swelling degree and drug release will be increased with an increase in pH. Particularly this study focuses on the effect of polymer ratio (κ-CG/SCMC), concentration of crosslinker and gelation time on drug release behavior. Ibuprofen (IB) was selected as a model drug. There is no previous research work done on IPN beads of κ-CG and SCMC using $AlCl_3$ as a crosslinking agent which makes this work a new of its kind in the development of pH responsive IPN beads of IB.

2. Experimental

2.1. Materials

IB was obtained from Yarrow Chemicals Products, Mumbai, India. κ-CG was purchased from Sigma–Aldrich Productions, GmbH, Germany. Sodium carboxy-methyl cellulose (SCMC: high viscosity of 2%, 3000–5000 mPa at 20 °C) and aluminium chloride were purchased from Hi-Media Laboratories Private Limited, Mumbai, India. Tween 80, barium chloride, zinc chloride, ferric chloride and calcium chloride were supplied by Loba Chemie Pvt. Ltd., Mumbai, India. All other reagents were of analytical grade.

2.2. Preparation of placebo IPN beads

Placebo or blank IPN beads were prepared by different ratio of κ-CG and SCMC (1:1 and 1:2). An aqueous solution of κ-CG and SCMC was prepared and the resulting gum solution was added dropwise through a 21 gauge flat tipped hypodermic needle into slightly agitated aqueous metallic salt solution (100 ml) containing 0.4% w/v Tween80. Different metallic salt solutions (barium chloride, zinc chloride, ferric chloride, calcium chloride and aluminium chloride) were used in concentrations ranging from (4% w/v and 6% w/v). Gelation of beads was carried out at different time periods (30 min and 60 min). The capability of different metallic salt solutions to form self-standing and segregable beads was examined. It was observed that the beads were formed immediately in the presence of trivalent Al^{3+} ions in both the concentrations. The beads were, then isolated by filtration and washed with distilled water and dried at 40 °C in hot air oven to constant weight. Prepared beads were kept in vacuum desiccators until used.

2.3. Preparation of drug loaded IPN beads

IPN beads of k-CG and SCMC containing Ibuprofen were prepared by water-in-water emulsion gelation process using $AlCl_3$ as a cross-linking agent. An accurately weighed quantity of IB corresponding to 30% of the dry mass of the polymer was dispersed in an aqueous solution of κ-CG and SCMC (total polymer concentration 2% w/v) and mixed homogeneously. The dispersion was added dropwise through a 21gauze flat tipped hypodermic needle into a slightly agitated aqueous solution of $AlCl_3$ (100 ml) containing Tween 80 (0.4% w/v). Drug loaded beads were held in a crosslinker solution for an incubation period of 30 min or 60 min and after that the beads were removed and washed with distilled water repeatedly to make them free from un-reacted ions and dried at 40 °C in a hot air oven. The dried beads were kept in vacuum desiccator until used. The beads were prepared using the following variables: a) The total polymer concentration was 2% w/v and κ-CG to SCMC weight ratio was varied to 1:1 (% w/v) and 1:2 (% w/v) respectively; b) Concentration of crosslinker ($AlCl_3$) solution varied from 4 to 6% w/v; c) The gelation time was varied from 30 min to 60 min. The composition of κ-CG: SCMC blended IPN beads are shown in Table 1. A proposed scheme for the formation of IPN is given in Fig. 1A.

2.4. Drug-polymer interaction

Fourier transform infrared (FTIR) spectra of pure drug, placebo beads and drug-loaded beads were recorded in a Shimadzu FTIR Spectrophotometer (Model FTIR-8400S, Shimadzu, Japan). The prepared IPN beads were crushed and mixed with KBr and converted into pellet at 100 kg pressure using a hydraulic press pellet technique in the wave region of 400–4000 cm^{-1}.

2.5. Differential scanning calorimetry (DSC) analysis

DSC thermogram of κ-CG, SCMC, pure drug, placebo beads and drug-loaded beads were recorded using Perkin–Elmer instrument (Pyris-Diamond TG/DTA, Singapore) which was calibrated against indium. Accurately weighed amount of sample (6 mg) was kept into a 50 μl aluminium pan in a hermetically sealed condition. The measurements were performed in an atmosphere of nitrogen (20 ml/min) between 30 and 500 °C at a heating rate of 10 °C/min.

2.6. X-ray diffraction (XRD) analysis

Qualitative XRD study was performed using X-ray diffractometer (Ultima III, Model: D/Max 2200, Rigaku Corporation, Japan). Pure drug, blank beads and drug-loaded beads were scanned from 0 to 50 °C at a diffraction angle of 2θ range under the following conditions: Source, Ni-filtered Cu-Kα (λ = 1.54) radiation; voltage, 40 kV; Current, 30 mA; scan speed, 5°/min.

2.7. Surface morphology analysis

The purpose of SEM study is to obtain topographical characteristics of the beads. Dried placebo and drug-loaded beads were examined under scanning electron microscope (JEOL-JSM- 6360, JEOL Datum Ltd, Tokyo, Japan). SEM photographs of uncoated samples were taken at a chamber pressure of 1.0 mm Hg and acceleration voltage of 17 kV.

2.8. Bead size analysis

The size of drug loaded IPN beads was measured using an optical microscope (Olympus Model HB, India). The eyepiece micrometer was calibrated with the help of a standard stage micrometer. Beads were placed on a glass slide and the number of divisions of the calibrated eyepiece was counted. The Individual particle diameter was calculated based on the formula: