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Controlled release of tinidazole and theophylline from chitosan based composite hydrogels

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ABSTRACT

Several composite hydrogels were synthesized by free radical crosslink copolymerization of acrylic acid (AA) and N′ methylene bis-acrylamide (MBA) in the presence of chitosan (CS). During polymerization CS was incorporated in situ in the crosslinked polyacrylic acid gel to produce composite hydrogels. The structure and properties of the hydrogels were characterized by FTIR, ^{13}C NMR, DTA–TGA, XRD, swelling and diffusion characteristic and also network parameters. The loading and the in vitro release behaviours of theophylline and tinidazole model drugs were studied with these hydrogels. The wt% of CS and MBA and pH of the medium was found to strongly influence the drug release behaviour of the gels. Accordingly, the release rate of these two drugs was much faster at pH of 7.6 than at pH 1.5.

1. Introduction

Most of the hydrogels are widely used as drug carrier because of its high swelling in water, soft pliable nature, biocompatibility and biodegradability. It can absorb large quantities of water or physiological solutions while the absorbed solutions are not removable even under pressure. In the swollen state, these gel networks become soft and rubbery, resembling a living tissue. No additional treatment is required for removal of these biodegradable delivery systems after end use (Bertza et al., 2013). These smart polymers are obtained by covalent crosslinking or non-covalent crosslinking of natural or biocompatible synthetic polymers (Islam & Yasin, 2012). Natural polymers are abundant and thus less expensive. Further, these polymers are non-toxic, biocompatible and biodegradable. However, hydrogels based on natural polymer are of poor mechanical strength (Ahn, Choi, & Cho, 2001; Lorenzo, Fernandez, Puga, & Concheiro, 2013). On the other hand most of the hydrogels based on synthetic polymers are mechanically durable but not biodegradable. Further, these synthetic hydrogels are expensive and also vulnerable to shear degradation (Sionkowska, 2011). Thus, hydrogels made by combining biocompatible synthetic polymers like various acrylic polymers with natural or semi-synthetic biopolymers based on polysaccharides or proteins have been widely explored to achieve high concentration of drugs in the specific region or tissue and the controlled release profile for extended time periods (Bertza et al., 2013; Matricardi, Meo, Coviello, Hennink, & Alhaique, 2013; Zhou, Zhang, Zhang, & Chen, 2011). For preparing gel a natural polymer and a synthetic polymer may be combined by some chemical reactions like grafting of a synthetic polymer on a natural polymer (Sokker, Abdel Ghaffar, Gad, & Aly, 2009; Zhang, Wang, & Wang, 2007), IPN formation by crosslinking one or both polymers (Yanga, Chena, Pana, Wanc, & Wang, 2013; Yue, Sheng, & Wang, 2009; Zhang et al., 2007), semi-IPN microspheres blend formation from natural and synthetic polymers such as polyvinyl alcohol and hydroxyethyl cellulose (Sullad, Manjeshwar, & Aminabhavi, 2010a, 2010b), gelatin and hydroxyethyl cellulose (Kajjari, Manjeshwar, & Aminabhavi, 2011) by emulsion crosslinking, in situ polymerization of a monomer in the presence of a natural polymer, etc. (Samanta & Ray, 2014). In grafting the synthetic monomer in small quantity is allowed to polymerize in the matrix of a base or trunk polymer where the monomer polymerize as well as form chemical bond with the base polymer. Free radicals are also generated on the base polymer and the macroradicals take part in graft copolymerization with the monomer. Crosslinking also occurs by formation of chemical bonds among macroradicals of the base polymer (Panic, Madzarevic, Husovic, & Velickovic, 2013; Wang & Wang, 2010). For producing a stable gel network there should be a good balance of grafting and crosslinking. However, highly reactive macroradicals or monomer radicals like acrylic radicals cause more of grafting and homopolymerization than crosslinking (Bhattacharya, Rawlins, & Ray, 2009). Further, the base polymer in a graft copolymerization is selective only to a

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specific number of monomers. Another way of combining a natural and synthetic polymer is to polymerize small amount of a synthetic monomer in aqueous solution of a natural polymer. However, for free radical solution polymerization, total monomer concentration in water should be at least 15–20 wt% (Samanta & Ray, 2014) while it is difficult to make an aqueous solution of a natural polymer with polymer concentration >5 wt% because of its high molecular weight and thus high viscosity of the solution. Thus, modifying a hydrogel of a natural polymer with a synthetic polymer by in situ polymerization of small amount of a synthetic monomer is difficult. Hence, semi- and full IPN type composite hydrogels are made by in situ incorporation of a natural polymer in the polymerization reaction mixtures of synthetic monomers. Accordingly, in the present work CS was incorporated in polyacrylic acid gel by in situ incorporation during crosslink copolymerization of acrylic acid and MBA in water. Acrylic acid monomer was chosen since its polymer viz. polyacrylic acid (PAA) is a pH responsive polyelectrolyte which has been extensively used for drug delivery to specific sites of gastrointestinal tract (Ahn et al., 2001). However, extensive swelling of uncrosslinked PAA in water limits its applications in drug delivery because of its dissolution before delivery of drug (Ahn et al., 2001). Thus, in the present work PAA was crosslinked with comonomer crosslinker MBA and subjected to interpenetration with CS for achieving stable network of a gel. MBA was chosen because of its use in drug delivery systems (Jameela, Lakshmi, James, & Jayakrishnan, 2002; Samanta & Ray, 2014). Among the various natural polymers CS was chosen because of its high molecular weight, high charge density and mucoadhesive properties leading to its wide spread use in drug delivery systems (Rao, Naidu, Subha, & Aminabhavi, 2006; Rokhade, Shelke, Patil, & Aminabhavi, 2007). In PAACS composite gel apart from crosslinking of PAA, a polyelectrolyte complex is also formed by electrostatic interaction of cationic CS and anionic PAA which increases further the stability of the gel. The hydrogels made from CS and PAA have also been reported by many researchers. A novel hydrogel made from CS, PAA and attapulgite was reported to show high swelling in water (Zhang et al., 2007). Torre et al. prepared hydrogel of CS and PAA by blending these two polymers in aqueous acetic acid solution followed by freeze drying to produce the network without any chemical crosslinking and amoxicillin drug was incorporated in situ in the blend network (Paloma, Torrea, Enobakharea, Torradob, & Torrado, 2003). Ahn et al. carried out template polymerization of acrylic acid in the presence of CS by UV radiation and this polyelectrolyte hydrogel was reported for transmucosal drug delivery system (Ahn et al., 2001). In a similar way, Shim and Nho prepared CS-PAA hydrogel without any chemical crosslinker by gamma radiation and this hydrogel was reported for release of 5-fluorouracil drug (Shim & Nho, 2003).

From the above discussion it is evident that hydrogels based on CS and PAA have been widely used for study of drug release. However, in these studies hydrogels were prepared either by blending PAA and CS or polymerizing acrylic acid in the presence of CS by UV or gamma radiations. In these gels no chemical crosslinkers have been used and stability of these gels depends on freeze drying and formation of polyion complexes between cationic CS (due to its NH_3^+ group) and anionic PAA. In the present work several hydrogels have been prepared by crosslink copolymerization of varied amounts of acrylic acid and MBA for obtaining stable gel networks. In these hydrogels varied concentrations of CS were incorporated in situ during polymerization and the resulting composite hydrogels were used for release of two important drug viz. tinidazole and theophylline. Tinidazole or 1-(2-ethylsulfonylethy)-L-2-methyl-5 nitroimidazole drug is mainly used for treatment of intestinal amoebiasis and other colon infections and also for periodontitis. However, this synthetic antibiotic has some potential hazards like peripheral neuropathy and convulsive seizures (Tracy & Webster, 1996). Thus, effective release of low dosage of this drug at colon using a colon targeted specific drug delivery system is desirable (Krishnaiah, Bhaskarreddy, Satyanarayana, & Karthikeyan, 2002). Because of good solubility in acidic medium, this drug is also expected to have good solubility in the present mucoadhesive PAACS hydrogel. Similarly, theophylline is a methylxanthine drug used as a bronchodialator for treatment of asthma and chronic obstructive pulmonary disease (COPD) by oral or intravenous route. However, clinical use of this drug is limited because of its adverse effects like nausea, vomiting, tachycardia, headache, seizure and agitation (Mastiholimath, Dandagi, Jain, Gadad, & Kulkarni, 2007). Thus, sustained delivery of the required concentration of the drug using a polymer hydrogel like the present PAA-CS composite gel would eliminate the side effects of the drug. Thus, in the present work the PAA-CS hydrogels were used for study of sustained release of these two important model drugs.

2. Materials and methods

2.1. Materials

Chitosan (CS) was kindly donated as free sample by Indian Sea Food, Cochin. It was used without any further purification. The comonomer crosslinker N,N′-methylene bisacrylamide (MBA, from Merck) and the redox pair of initiators ammonium persulfate (APS, from Fluka) and sodium metabisulfite were of analytical grade and used without any further purification. The monomer acrylic acid (AA, Merck) was used after vacuum distillation. The drugs theophylline and tinidazole were purchased from Loba Chemicals, Mumbai, India and used as obtained.

2.2. Methods

2.2.1. Preparation of hydrogel

At first PAA gels were prepared at varied initiator, total monomer (AA), crosslinker (MBA) concentration in a three necked reactor placed on a constant temperature bath and fitted with a stirrer, a thermometer pocket and a condenser at 30 °C. For preparing composite gel varied concentrations, i.e., 0.5, 1.0 and 2.0 wt% of CS was made in deionized water containing 2 wt% of acetic acid in a 250 mL glass beaker by gradual addition of required amount of CS to obtain a viscous solution of CS. The required amount of CS solution and AA monomer was then poured into the reactor. Temperature was maintained at 30 °C and aqueous solution of initiators was added to the reactor followed by the addition of MBA (crosslinker). After polymerization the reaction mixture was cooled to ambient temperature. Hydrogel obtained was cut into small blocks and then immersed into double distilled water for 48 h to remove water soluble oligomer, uncrosslink polymer and unreacted monomers from the gel. The gel obtained was dried in a vacuum oven at 60 °C to a constant weight. The dried gel, also called xerogel was then disintegrated in a blender.

2.2.2. Yield, sol and gel content of the hydrogel

The hydrogels as prepared above were first dried to a constant weight (m_c) in a vacuum oven and then it was taken in water and kept for a week with occasional shaking to remove the water soluble part from the hydrogel. The water insoluble gel sample was further dried (xerogel) in vacuum oven to a constant weight (m_d). Yield, gel and sol% was obtained as

$$\text{Yield\%} = \frac{m_c}{m_i} \times 100 \quad (1)$$

$$\text{Gel\%} = \frac{m_d}{m_c} \times 100 \quad (2)$$

$$\text{Sol\%} = 100 - \text{Gel\%} \quad (2a)$$