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Synthesis of dual responsive carbohydrate polymer based IPN microbeads for controlled release of anti-HIV drug

S. Eswaramma, K.S.V. Krishna Rao (Assistant Professor)*

Polymer Biomaterial Design and Synthesis Laboratory, Department of Chemistry, Yogi Vemana University, Kadapa, Andhra Pradesh, 516003, India

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ABSTRACT

The present study aims at preparation of dual responsive interpenetrating polymer network hydrogel microbeads from sodium alginate and functionally modified guar gum. Guar gum was modified by graft copolymerization using *N*-vinylcaprolactam, the maximum % grafting 123.2, obtained at different optimized conditions. The graft copolymer was blended with sodium alginate to form hydrogel microbeads by emulsion crosslinking method using glutaraldehyde as crosslinker. Zidovudine, an anti-HIV drug was encapsulated with 68% encapsulation efficiency. Fourier transform infrared spectroscopy, ^{1}H nuclear magnetic resonance spectroscopy, scanning electron microscopy, differential scanning calorimetry and X-ray diffraction studies justified the grafting reaction, structure, morphology and polymer-drug interactions, respectively. Swelling studies ascertained that microbeads were potentially sensitive to both pH and temperature. *In vitro* release studies were investigated in pH 1.2 and 7.4, the release time enhanced up to 34 h in pH 7.4 at 37 °C.

1. Introduction

Since past few decades, a wide range of both synthetic and carbohydrate polymers have been extending their enormous applications in pharmaceutical and biomedical fields exclusively for controlled drug release studies (Chen, Gao, Qiu, & Hu, 2013; Kang, Cheon, & Song, 2006; Makadia & Siegel, 2011; Sutar, Mishra, Pal, & Banthia, 2008). Of these, carbohydrate polymers hold a great promise for biomedical research over synthetic polymers due to their inherent properties such as inexpensiveness, non-toxicity, biodegradability and biocompatibility, since they are originated from natural sources (Dang & Leong, 2006) (Kumbar & Aminabhavi, 2003). Among various controlled release devices, IPN hydrogel microbeads have been preferred due to their unique properties such as particle size, phase stability and mechanical strength (Freiberg & Zhu, 2004), which would be able to encapsulate wide range of drugs with high pay load.

Sodium alginate (NaAlg), is a well known sodium salt of alginic acid, one of the most abundant naturally occurring carbohydrate polymers, usually extracted from all the species of brown algae and some specific species of bacteria. Chemically alginates are linear anionic polysaccharides consist β-D-mannuronate and α-L-guluronate residues joined together by (1-4)-glycoside linkages (Işıklan, Inal & Yiğitoğlu, 2008; Olukman & Solak, 2012; Soni, Kumar, & Namdeo, 2010). As these alginates posses carboxyl groups, the resulting polymer network exhibits pH responsive behaviour that provide a proper way for pH- responsive drug release (Shaikh et al., 2010). Previous studies reported the utilization of various alginate based systems to investigate different biomedical applications. Reddy et al. developed pH responsive alginate based hydrogel nanocomposites for the release of 5-fluorouracil and also used to study anti bacterial activities (Reddy, Rao, Rao, Shchipunov, & Ha, 2014). Rastogi et al. fabricated spherical microspheres of alginate to sustain the release of isoniazid (Rastogi et al., 2007). Chitosan-sodium alginate nanoparticles were used to improve the ophthalmic delivery of gatifloxacin, through the formation of polyionic species (Motwani et al., 2008).

Guar gum (GG) is another excellent water soluble carbohydrate polymer, derived from the seeds of Cyamposis tetragonoloba (Leguminosae). GG is a galactomannan consisting of a non-ionic, linear backbone of (1-4) linked β-D-mannopyranose units, on which single membered α-D-galactopyranosyl units are branched randomly (Sullad, Manjeshwar, & Aminabhavi, 2010). Since GG has large rate of hydration, it readily forms highly viscous solutions in water, due to this it has been employed in various industrial and biomedical applications (Kalia & Sabaa, 2013; Kobayashi, 2012). However these applications of GG have greatly limited because of its uncon-

* Corresponding author.
E-mail addresses: ksvkr@yogivemanauniversity.ac.in, drksvkrishna@yahoo.com (K.S.V.K. Rao).

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trolled rate of hydration, reduced viscosity upon storage and rapid microbial contamination. In order to overcome the above limitations and also to improve the physical and chemical properties of GG, researchers have been explored different polymer modification techniques such as derivatization, grafting and formation of gel network (Gupta & Warkar, 2015; Hiremath, Vishalakshi, & Mangalagangothri, 2014). Among these methods, grafting copolymerization has been widely performed to modify both the physical and chemical properties of GG.

In the existing literature, a wide range of carbohydrate polymers have been grafted with various synthetic monomers to introduce required properties (Al-Karawi & Al-Daraji, 2010; Enomoto-Rogers & Iwata, 2012; Fares, Assaf, & Abul-Haija, 2010; Mishra, Sand, Mishra, Yadav, & Behari, 2010; Prasad et al., 2012; Qiu, Feng, Wu, Zhang & Zhuo, 2009; Rao, Rao, Kumar, & Chung, 2010; Sadeghi & Heidari, 2011; Wang & Wang, 2010) that are suitable for controlled drug delivery applications. In the graft copolymerization process, the guest monomer and the host polymer interactions can be initiated by a variety of initiators (Fares, Assaf, & Abul-Haija, 2010; Huacai, Wan, & Dengke, 2006; Kiatkamjornwong, Mongkolsawat, & Sonsuk, 2002; Kim, Cho, Lee, & Kim, 2000; Wang & Wang, 2010; Thakur & Singha, 2010).

Polymers that are sensitive to external stimuli such as temperature, pH, ionic strength *etc.* are known as "smart" or "intelligent" polymers. Among those responsive polymers, Poly(N-vinylcaprolactam) (PNVCL) is one of the most attracted and well studied thermo-responsive polymers. PNVCL is a non-ionic, water-soluble, non-toxic and biocompatible polymer, has lower critical solution temperature (LCST) in the range of 32–34 °C, which is very close to the physiological body temperature (37 °C) (Boyko, 2004; Cheng et al., 2002; Dalton, Halligan, Killion, Murray, & Geever, 2014). Below LCST, the polymer undergoes hydration and becomes swell but above LCST, it gets precipitation due to dehydration process (Kozanoglu, 2008; Ponce-Vargas, Cortez-Lemus, & Licea-Claveríe, 2013). Due to its thermo-responsiveness and biocompatibility, PNVCL has been prominently employed for biomedical applications (Rao, Rao, & Ha, 2016).

Zidovudine, chemically known as azidothymidine (AZT), a nucleoside reverse transcriptase inhibitor, the first approved antiretroviral drug. The therapeutic usage of AZT is seriously limited by its hematological toxicity due to high dosage levels of drug, low therapeutic index, very short biological half life (1–3 h) and poor oral bioavailability (60%). During the conventional release of AZT, patients have been receiving many side effects such as anemia, leucopenia and low patient compliance (Kar, Mohapatra, & Barik, 2009; Mohima, Dewan, Islam, Rana, & Hossain, 2015; Nayak et al., 2009). To minimize all these side effects and to maintain the constant therapeutic drug level, the controlled release formulations were introduced and developed, which would be more beneficial and more flexible to provide desirable drug release profiles over conventional methods.

Now a day, researchers have been extending their research towards functional modification of carbohydrate polymers to enhance the mechanical properties, biocompatibility and responsiveness. Realizing from the existing literature of the modification of carbohydrate polymers, we found that no attempts have yet been made to graft PNVCL on GG backbone. Keeping in this view, first time we reporting the modification of carbohydrate polymer GG by incorporating PNVCL chains on GG back bone *via* free radical grafting mechanism. Next, we have formulated IPN hydrogel microbeads of NaAlg and GG-*g*-PNVCL by water-in-oil emulsion crosslinking method and were used as controlled delivery devices for AZT, an antiretroviral/reverse transcriptase inhibitor. *In vitro* AZT release studies were examined in both acidic (pH = 1.2) and alkaline (pH = 7.4) media at temperatures above and below LCST of NVCL (*i.e.* 25 °C and 37 °C), that support better understanding release profiles of AZT in stomach and intestine as well. Korsmeyer-Peppas model equation was attributed to assess the release kinetics of IPN microbeads under different pH and temperature conditions.

2. Experimental

2.1. Materials

N-Vinylcaprolactam (NVCL) was purchased from Aldrich chemicals co. U.S.A. Guar gum (GG) was purchased from Merck, India. Sodium alginate (NaAlg) was purchased from CDH, India. Potassium persulphate (KPS) and glutaraldehyde (GA) were purchased from sd-fine chemicals, India. The anti-HIV drug, Zidovudine (AZT, purity >97%) was kindly gifted by Ildoo Chung, Pusan National University, Pusan, South Korea and the same was received the AZT from Samchully Pharmaceutical Company (Seoul, South Korea). All the chemicals were used without further purification and solvents were of analytical grade. Double distilled (DD) water was used throughout the experimental pathway.

2.2. Synthesis of guar gum-g-poly(N-vinylcaprolactam)

The graft polymerization reaction of GG and PNVCL was followed by the procedure reported in the earlier literature (Prasad et al., 2012). Briefly, 0.50 g of GG was dispersed in 30 mL of distilled water in a 250 mL round bottom flask, which was kept for hydration for 24 h with continuous stirring. Then 3.5922×10^{-3} to 10.7766×10^{-3} moles of NVCL were dissolved in 10 mL distilled water and this solution was added to the above GG solution and stirring is maintained moderately for 1 h to get the homogenous solution. To this homogenous solution, 0.7399×10^{-3}–2.2196×10^{-3} moles of KPS are added and the polymerization was carried out at 40–60 °C for 0.5–4 h in a water bath. Nitrogen is continuously purged before the addition of initiator. After the polymerization reaction was completed, the obtained reaction mixture was first cooled to room temperature and then poured into acetone to obtain white solid graft copolymer by eliminating the unreacted monomer and initiator. If any homopolymer of NVCL was formed during the polymerization process, it was removed by washing the graft copolymer with methanol-water mixture (4:2) for several times. The final solid obtained was first filtered and then dried at 40 °C until get constant weight. The structural representation of the graft copolymer (GG-*g*-PNVCL) has shown in Fig. S1. The grafting parameters were calculated using the following equations and are depicted in Table S1.

$$\%\text{Grafting}\,(\%G) = \left(\frac{W_1 - W_0}{W_0}\right) 100 \quad (1)$$

$$\%\text{Graftingefficiency}\,(\%GE) = \left(\frac{W_1 - W_0}{W_2}\right) 100 \quad (2)$$

$$\%\text{Conversion}\,(\%C) = \left(\frac{W_1}{W_2}\right) 100 \quad (3)$$

Where, W_0, W_1 and W_2 denote the weight of GG, GG-*g*-PNVCL and NVCL, respectively.

2.3. Preparation of NaAlg-(GG-g-PNVCL) IPN hydrogel microbeads

IPN hydrogel microbeads of NaAlg and GG-*g*-PNVCL were prepared by well established water-in-oil (w/o) emulsion crosslinking method using glutaraldehyde (GA) as crosslinker (Rao, Naidu, Subha, Sairam, & Aminabhavi, 2006). Firstly, 20 mL of 2% (w/v) polymer solution was prepared by dissolving different ratios of NaAlg and GG-*g*-PNVCL in DD water and the solution is allowed to stir for overnight to get homogenesity. Later the blend polymer solution