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Synthesis and characterization of semi-interpenetrating polymer network microspheres of acrylamide grafted dextran and chitosan for controlled release of acyclovir ☆

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Abstract

Semi-interpenetrating polymer network (IPN) microspheres of acrylamide grafted on dextran (AAm-*g*-Dex) and chitosan (CS) were prepared by emulsion-crosslinking method using glutaraldehyde (GA) as a crosslinker. The grafting efficiency was found to be 94%. Acyclovir, an antiviral drug with limited water solubility, was successfully encapsulated into IPN microspheres by varying the ratio of AAm-*g*-Dex and CS, % drug loading and amount of GA. Microspheres were characterized by FT-IR spectroscopy to assess the formation of IPN structure and to confirm the absence of chemical interactions between drug, polymer and crosslinking agent. Particle size was measured using laser light scattering technique. Microspheres with average particle sizes in the range of 265–388 μm were obtained. Differential scanning calorimetry (DSC) and X-ray diffraction (X-RD) studies were performed to understand the crystalline nature of drug after encapsulation into IPN microspheres. Acyclovir encapsulation of up to 79.6% was achieved as measured by UV spectroscopy. Both equilibrium and dynamic swelling studies were performed in 0.1 N HCl. Diffusion coefficients (D) and diffusional exponents (n) for water transport were determined using an empirical equation. In vitro release studies indicated the dependence of drug release rates on both the extent of crosslinking and amount of AAm-*g*-Dex used in preparing microspheres; the slow release was extended up to 12 h. The release rates were fitted to an empirical equation to compute the diffusional exponent (n), which indicated non-Fickian trend for the release of acyclovir.

Keywords: Hydrogels; Crosslinking; Graft copolymer; Interpenetrating polymer networks; Drug delivery systems; Microspheres; Acyclovir

1. Introduction

Hydrogels are the three-dimensional network polymers that are known to swell in aqueous solutions. In the swollen state, they are soft and rubbery, resembling the living tissue exhibiting excellent biocompatibility (Hoffman, 2002). Polymeric hydrogels are of considerable interest as biomaterials in drug delivery research (Coviello et al., 2005; Liu, Lin, Lin, & Liu, 2005; Peppas, Bures, Leobandung, & Ichikawa, 2000; van Tomme, van Steenbergen, De Smedt, van Nostrum, & Hennink, 2005). In pharmaceutics area, carbohydrate polymers are often preferred over synthetic polymers due to their non-toxic, low cost, ease of availability and biodegradability characteristics. The hydrogels of modified carbohydrate polymers have been extensively used in controlled release (CR) applications of pharmaceutical proteins as well as in tissue engineering (Chen et al., 2004; Franssen, Vandervennet, Roders, & Hennink, 1999). Among many methods of modifying the original structure of polymers, graft copolymerization is an easier method, which makes the derived polymer as attractive biomaterials in CR applications (Soppimath & Aminabhavi, 2002).

Among the many natural carbohydrate polymers, dextran (Dex) is a polysaccharide consisting of glucose

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molecules coupled into long branched chains, mainly through 1,6- and some through 1,3-glucosidic linkages. Dextrans are colloidal, hydrophilic and water-soluble substances that have excellent biocompatibility and hence, they do not affect cell viability. Because of these properties, dextrans have been used as blood expanders to maintain or replace blood volume. Dextrans are also used as carriers to study the CR of a variety of therapeutic agents including antidiabetics, antibiotics, anticancer drugs, peptides and enzymes (Hennink, De Jong, Bos, Veldhuis, & van Nostrum, 2004; Kosmala, Henthorn, & Peppas, 2000; Stenekes & Hennink, 1999). Dextrans can be degraded by the dextranase enzyme, which is present in colon (Hovgaard & Brondsted, 1995). Chitin, a poly-β-(1 → 4) linked *N*-acetyl-D-glucosamine, is a polysaccharide widely distributed in nature, whereas chitosan (CS) is obtained by deacetylation of chitin. Chitin and CS are the well-known biocompatible and biodegradable carbohydrate polymers that are widely used in biomedical applications (Berger et al., 2005) including wound dressings and drug delivery systems (Lu, Steenekamp, & Hamman, 2005). Chitosan has many pharmaceutical applications (Kumar, Muzzarelli, Muzzarelli, Sashiwa, & Domb, 2004) as a bioadhesive polymer (Agnihotri & Aminabhavi, 2004; Hejazi & Amiji, 2003). However, the biodegradation characteristics of CS are dependent upon the degree of deacetylation.

Acyclovir, previously known as acycloguanosine, has potent inhibitory effects on viruses of the herpes group, particularly herpes simplex virus (HSV, I and II) and herpes zoster varicellaous virus. It also combines inhibitory effects on hepatitis B virus with very low toxicity to mammalian host cells (Haynes, Lambert, & Mitchell, 1996). Various reports have indicated that acyclovir is as effective as or even superior to other antiviral agents with lower host toxicity and milder side effects (Tu, Wang, Yang, Fei, & Li, 2001). Since acyclovir has a short half-life (2–3 h), and its oral dosage forms must be taken five times daily, which is very inconvenient for patients. Hence, researchers have been studying the CR applications of acyclovir (Rossi, Sandri, Ferrari, Bonferoni, & Caramella, 2003a, Rossi, Sandri, Ferrari, Bonferoni, & Caramella, 2003b; Sandri et al., 2004). The principle objective of this study is to develop CR formulations of acyclovir that may be taken twice daily. In this paper, we report the synthesis of pAAm-*g*-Dex to prepare the IPN microspheres with CS crosslinked by GA for the CR of acyclovir. The IPNs are a combination of two or more polymers in a network form that are held together by topological bonds without the formation of covalent bonds between them (Kim & Sperling, 1997). Thus, an IPN structure can be obtained when at least one polymer network is synthesized and/or crosslinked independently in the immediate vicinity of another. As long as the reacting ingredients are blended thoroughly during the synthesis, thermodynamic incompatibility can be made to overcome due to the permanent interlocking of the network segments. Hence, IPN based systems have gained good potential to develop the CR systems.

Earlier, we have reported many IPN-based formulations for the CR of a variety of drugs (Agnihotri & Aminabhavi, 2005; Kurkuri & Aminabhavi, 2004; Rokhade et al., in press; Soppimath, Kulkarni, & Aminabhavi, 2000). In continuation of these studies, we now present synthetic protocols for the preparation of semi-IPN microspheres of acrylamide grafted dextran and CS for the CR of acyclovir. The microspheres formed have been characterized by FT-IR, X-RD and DSC techniques. In vitro release studies have been performed by dissolution experiments. Release data have been discussed in terms of Fickian equation and diffusion parameters.

2. Experimental

2.1. Materials

Acyclovir was obtained as a gift sample from Matrix Laboratories, Hyderabad, India. Dextran, MW ≈ 85,000 was purchased from Hi-media Chemicals Pvt. Ltd., Mumbai, India. CS was procured from Aldrich Chemical Company, Milwaukee, WI, USA. Analytical reagent grade acrylamide, glutaraldehyde solution 25% (v/v), ceric ammonium nitrate, *n*-hexane and light liquid paraffin were all purchased from s.d. fine Chemicals, Mumbai, India. Span®-80 was purchased from Loba Chemicals, Mumbai, India. All the chemicals were used without further purification.

2.2. Synthesis of graft copolymer of dextran–acrylamide

The graft copolymer of dextran and acrylamide was prepared by free radical polymerization. Briefly, 2 g of dextran was dissolved in 70 mL of water and allowed to stir overnight in a 250 mL round-bottom flask. Then, 0.12 mol of AAm was separately dissolved in 20 mL water, which was added to dextran solution and allowed to mix uniformly for 1 h. To this solution, 10 mL of 5 mM ceric ammonium nitrate was added. Polymerization was carried out at 60 °C under a continuous purging of nitrogen gas for 6 h in a water bath with constant stirring. After complete polymerization, a sufficient amount of methanol was added to precipitate the graft copolymer and to remove any homopolymer formed. The polymer was dried under vacuum (60 mmHg pressure) at 40 °C overnight. Mass of the polymer was taken and % grafting efficiency was calculated as

$$\%\ \textit{Grafting efficiency}\ (\%GE) = \left(\frac{W_1 - W_0}{W_2}\right) \times 100, \qquad (1)$$

where W_0, W_1 and W_2 denote weights of dextran, graft copolymer and monomer, respectively. The synthetic scheme for the formation of graft copolymer is shown in Fig. 1.