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Network formation of Moringa oleifera gum by radiation induced crosslinking: Evaluation of drug delivery, network parameters and biomedical properties

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ABSTRACT

The present article is an attempt to explore the potential of the Moringa *oleifera* gum polysaccharides in network formation with poly(acrylic acid) by radiation induced crosslinking to develop the hydrogel for slow drug delivery applications. Polymers were characterized by Cryo-SEM, AFM and ^{13}C NMR techniques. Furthermore, drug delivery, network formation and some biomedical properties like blood compatibility, antioxidant activity, mucoadhesion and gel strength of the hydrogels were also determined. The release of ciprofloxacin occurred through non-Fickian diffusion mechanism and release profile best fitted in Korsmeyer-Peppas kinetic model. The hydrogels were found to be pH responsive, mucoadhesive non-thrombogenic, non-haemolytic, and antioxidant in nature. The crosslink density (ρ) and the mesh size (ξ) of the polymer network was observed 3.81×10^{-5} mol/cm^3 and 38.77 nm respectively in pH 7.4 solution.

1. Introduction

Radiation induced crosslinking is a well-established technique for developing sterile and pure hydrogels for biomedical applications. Herein this technique, hydrogel formation does not require chemical initiator and crosslinker. It is a single step process wherein gel formation and sterilization takes place simultaneously [1–3]. It is easy technique to regulate the drug delivery by controlling crosslinking density and swelling of the hydrogel [4]. It is superior, cost effective and efficient method of hydrogel synthesis as compared to chemical method [5].

Radiation crosslinking of hydrophilic vinylic monomer with polysaccharides gum led to the formation of hydrogels which have combined chemical and physical properties of both the components [6,7] Ionizing radiation causes chain scission of polysaccharides in the absence of crosslinking agents. It has been found that before that degradation of polysaccharides may be prevented, despite presence of strong electrostatic repulsing forces between chains, at very high polymer concentration in water (paste-like state) when physical proximity promotes recombination of radiation generated polymer radicals. In such conditions, crosslinking dominates over chain scission and covalent, macroscopic gels can be formed [8–10]. Hydrogels are hydrophilic, three dimensional polymeric networks which swell quickly by imbibing large quantity of water or de-swell in response to changes in their external environment. Hydrogels are excellent choices as biomaterials in the drug delivery due to their biocompatibility and volume phase transitions arising due to change in polymer-solvent interactions as a response to different stimuli [11]. Peppas and coworkers have reported the various biomedical and pharmaceutical applications of the hydrogels [12,13]. The utilization of natural polysaccharides in drug delivery continues to be a subject of intense investigation their biodegradability and biocompatibility. Various polysaccharide, like chitosan, pectin, chondroitin sulphate, cyclodextrin, dextran, guar gum, inulin, amylose and locust bean gum, have been used in colon specific drug delivery [14,15]. Drug delivery to the colon is desired not only for oral delivery of peptide and proteins but also to treat different diseases associated with the colon such as irritable bowel syndrome, colon cancer, colitis, and ulcerative colon.

In the present work an attempt has been made for network formation of natural polysaccharide *Moringa oleifera* (MO) gum in the presence of network – forming monomer acrylic acid by radiation induced crosslinking. Crosslinking of polyacrylic acid onto MO will

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form the hydrogel for slow release of model drug 'ciprofloxacin' which is a broad spectrum antibiotic used for the treatment of the various bacterial infections in the human beings.

MO gum has also been used as a pharmaceutical excipient in oral mucoadhesive drug delivery systems [16]. Swelling has been found as a primary mechanism in these diffusion controlled release dosage form [17]. MO gum has been used as binder, disintegrants and release retardant in tablet formulation. In case of its application as binding agent in chloroquine tablet, increase in hardness, increase in disintegration time, decrease in percentage friability and decrease in percentage cumulative release have been observed with increase in gum content in the formulation as compared to the potato starch [18]. In case of its sustained release dosage formulations of diclofenac sodium, formulation maintained therapeutic blood levels of the drug for an extended and specified period of time [19]. In case of mucoadhesive buccal tablet composed of metaprolol tartarate, it was used as a binding agent [20]. MO gum has been reported to have gel forming potential for topical application. Its transdermal films loaded with neomycin drug has been used in wound dressing application [21].

Moringa oleifera (MO) is an important medicinal herb, belonging to the family Moringaceae. All the parts of the plant are useful for human health and contain vitamins, minerals and various antioxidants [22]. MO gum is used in the treatment of diarrhea besides its diuretic and blood lowering effect [22,23]. In India, MO gum is commonly recognized as sajna gum. This polysaccharide gum has a molecular weight of 190 kDa. It contains L-arabinose, -galactose, -glucuronic acid, and L-rhamnose, -mannose and -xylose [24,25]. Raja and coworkers [25] have reported the isolation, purification and fine structure of an arabinogalactan from MO gum and evaluated the antioxidative activity of this polymer.

Poly(acrylic acid) is a pH-sensitive synthetic polymer which is used potentially in the colon specific delivery of drugs to the specific regions of the gastrointestinal tract (GIT). Introduction of the anionic functional groups –COOH onto natural polysaccharide make the polymer matrix pH-sensitive and potential candidate for site specific drug delivery [26]. Furthermore, there exist different intermolecular interactions, like electrostatic, dipole-dipole interaction and hydrogen bonds, polyacrylic acid with polysaccharides which are also responsible for make it suitable candidate for pharmaceutical preparations particularly in slow the drug delivery systems [27]. Huang et al. [27] have prepared the ketoprofen loaded guar gum/polyacrylic acid hydrogels. The compositions of the hydrogel showed an important effect on ketoprofen release. The increase of polyacrylic acid content conduced to the rapid release of ketoprofen from the hydrogels. The pH of the dissolution medium appeared to have a strong effect on the drug transport mechanism.

In view of the above, in the present work MO based hydrogels have been developed and these polymers were characterized by Cryo-SEM, AFM and ^{13}C NMR techniques. Furthermore, drug delivery, network formation and some biomedical properties like blood compatibility, antioxidant activity, mucoadhesion and gel strength of the hydrogels were also determined

2. Experimental

2.1. Materials used

Acrylic acid (AAc) was obtained from Merck Specialities Private Limited (Mumbai, India). Moringa *oleifera* [MO] gum was obtained as a gift from Nutramine Life Sciences-Delhi, India. Folin–Ciocalteu (F–C) reagent was purchased from [Merck Specialities Private Limited, Mumbai, India], and 2,2-diphenyl-1-picrylhydrazyl (DPPH) was purchased from [Sigma–Aldrich, Munich, Germany].The model drug used in present studies i.e. ciprofloxacin hydrochloride (Abbott healthcare private limited, Mumbai, India) was procured from the market. All the materials are used as they received.

2.2. Synthesis of MO-cl-poly(AAc) polymers

The synthesis of the polymers was carried out by radiation induced cross-linking method. Solution of definite concentration of MO gum (12.5% w/v) in distilled water was taken in a beaker. A definite amount of acrylic acid (16.99×10^{-1}) was added to it and reaction mixture was kept for hydration in a water bath at 37 °C temperature. The reaction mixture was then stirred at 100 rpm speed with overhead stirrer for two hours to get a homogenous reaction mixture. The solution was then irradiated in gamma chamber (^{60}Co-rays) for a period of definite time interval at 0.610 kGy/h radiation dose. The polymer samples were washed with distilled water to remove the soluble fractions left after completion of reaction and then dried in air oven at 45 ± 2 °C until constant weight is achieved by the polymer sample. These polymer samples were named as MO-*cl*-poly(AAc) hydrogels. The optimum reaction parameters for the synthesis of hydrogels were evaluated by varying the amount of acrylic acid from 7.29×10^{-1} molL^{-1} to 16.99×10^{-1} molL^{-1} and radiation dose from 14.65 kGy to 43.93 kGy at fixed MO gum concentration = 12.5% (w/v). The optimum reaction conditions for synthesis of polymers were obtained as: [AAc] = 16.99×10^{-1} molL^{-1} and total radiation dose = 14.65 kGy. The optimum reaction conditions were determined on the basis of swelling of the hydrogels and surface consistency maintained by these hydrogels after 24 h swelling. Hydrogels prepared at optimum reaction conditions were used to determine network parameters, drug release profile and biomedical properties.

2.3. Swelling studies

Swelling studies of the hydrogels were carried out by gravimetric method [28]. Known weight of the hydrogel was taken and immersed in excess of the solvents for different time intervals at 37 °C. The hydrogels were then removed, wiped with tissue paper to remove excess of solvent and weighed immediately. Difference in the weight gave the gain in weight at different time intervals. Swelling of the hydrogels was determined by using Eq. (1).

$$\text{Swelling of hydrogels} = \frac{(W_s - W_o)}{W_o} \quad (1)$$

where W_o is initial weight of dry hydrogel and W_s is the weight of hydrogel after 24 h swelling. The swelling studies of the hydrogels were carried out in triplicate.

2.4. Determination of the network parameters

The release of drug from the drug loaded hydrogels is dependent on the swelling of the hydrogels which is controlled by network density and porosity of the hydrogels. The most important parameters used to portray network structure are the polymer volume fraction in the swollen state (φ), Flory-Huggins interaction parameter (χ), molecular weight of the polymer chain between two neighboring cross-links ($\overline{M}_c$), crosslink density (ρ) and the mesh size (ξ). $\overline{M}_c$ is the average molecular mass between the cross links and is linked directly to the cross linked density i.e. to the density of the intermolecular bond. The cross-linked structure of the prepared MO-*cl*-poly(AAc) hydrogels is studied by taking swelling of hydrogels in distilled water. The density of hydrogels was calculated by measuring the radius, height and weight of dry cylindrical hydrogel. To study the effect of reaction parameters on different network parameters, swelling of hydrogels at different (300.15, 310.15 and 320.15 K) temperatures was taken. The samples were allowed to swell to equilibrium in distilled water at different temperature and