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Synthesis and characterization of psyllium-NVP based drug delivery system through radiation crosslinking polymerization

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Abstract

In order to develop the hydrogels meant for the drug delivery, we have prepared psyllium-*N*-vinylpyrrolidone (NVP) based hydrogels by radiation induced crosslinking. Polymers were characterized with SEMs, FTIR and swelling studies. Swelling of the hydrogels was studied as a function of monomer concentration, total radiation dose, temperature, pH and [NaCl] of the swelling medium. The swelling kinetics of the hydrogels and release dynamics of anticancer model drug (5-fluorouracil) from the hydrogels have been carried out for the evaluation of swelling and drug release mechanism. It has been observed that diffusion exponent '*n*' have 0.8, 0.9, 0.8 and gel characteristics constant '*k*' have 9.22×10^{-3}, 2.06×10^{-3}, 11.72×10^{-3} values for the release of drug from the drug loaded hydrogels in distilled water, pH 2.2 buffer and pH 7.4 buffer, respectively. The present study shows that the release of drug from the hydrogels occurred through Non-Fickian diffusion mechanism.

Keywords: Radiation induced crosslinking; Hydrogels; Psyllium; Drug delivery

1. Introduction

Cancer of the colon is a major health problem and it ranks as a leading form of cancer, along with lung and breast cancer. Importantly, colon cancer is also one of the most curable forms of cancer. When detected early, more than 90% of patients can be cured. This disease begins in the cells that line the colon. There now is strong medical evidence that there are abnormal genes for colon polyps and cancer that can be passed from parent to child. The genes within each cell are the hereditary structures that tell the cell what it should do. When these controlling genes are absent, there is a tendency to grow polyps. The cells in the polyp eventually become uncontrolled and turn into a cancer. Colon cancer can also develop with other conditions, such as ulcerative colitis, a chronic inflammation in the colon. The human epidemiology indicates an inverse correlation between high-fiber consumption and lower colon cancer rates. Dietary fibers not only bind carcinogens, bile acids, and other potential toxins but also essential nutrients, such as minerals, which can inhibit the carcinogenic process. Beside its cancer curing property it has also been reported for the treatment of constipation, diarrhea, inflammation bowel diseases – ulcerative colitis and hyperglycemia [1–3]. Therapeutic response of the psyllium could be double if cancer curing agent released from the psyllium based drug delivery system. Polysaccharides based devices, especially hydrogels, are effective in enhancing drug targeting, lowering systemic drug toxicity and providing protection for pharmaceuticals against biochemical degradation.

Psyllium is obtained from the seed coat by mechanical grinding of the outer layer of the seeds. It is fibrous, hydrophilic and forms the clear gel by absorbing water. Its gel nature and composition has been reported in literature [4,5]. Fischer et al. [6] have studied the physiologically active, gel-forming fraction of the alkali-extractable polysaccharides of *Plantago ovata Forsk* seed and some

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derived partial hydrolysis products by compositional analysis, methylation analysis and NMR spectroscopy. Chemical and physical studies of the psyllium mucilage show that it has arabinose 22.6%, xylose 74.6% and traces of other sugars. With about 35% of non-reducing terminal residues, the polysaccharide is highly branched. The data are compatible with a structure consisting of a densely substituted main chain of β-(1→4)-linked D-xylopyranosyl residues, some carrying single xylopyranosyl side chains at position 2, others bearing, at position 3, trisaccharide branches having the sequence L-Araf-α-(1→3)-D-Xylp-β-(1→3)-L-Araf [6].

Hydrogels are three-dimensional polymeric networks which are formed by chemical or physical crosslinking. These are capable of imbibing large amounts of water or biological fluids. These become stimuli responsive when contain some specific functional groups and this property brings the volume phase transitions and makes these materials useful for advanced technologies [7–11]. Hydrogels, specially based on the polysaccharides, have attracted considerable attention to act as a smart candidate for the controlled release of therapeutic agents to the specific sites in the GI tract [12,13]. Sometimes incorporation of polysaccharides into the hydrogels increases their strength and equilibrium swelling [14]. Mathematical modeling plays an important role in facilitating hydrogel network design by identifying key parameters and molecule release mechanisms [15]. Swelling kinetics of the hydrogels and release dynamics of drug from the hydrogels depend on the matrix swelling which is further dependent on the composition of the hydrogels and pH of the swelling medium [16]. Molecular weight of the drug also affects the release profile of the drug from the hydrogels [17]. The rate of release of the theophylline has been observed faster from poly(2-hydroxyethyl methacrylate/itaconic acid) hydrogels composing of higher content of itaconic acid. This is due to the small molecular size and a weak interaction of the theophylline molecules within the copolymeric networks [18]. Irradiation dose has little influence on the thermo and pH-sensitivity of the interpenetrating polymer networks membrane of poly(*N*-isopropylacrylamide)/carboxymethyl chitosan and increasing dose has only decreased the swelling ratio [19].

Grafting and crosslinking has been common practice to improve the functional properties of polysaccharides and to develop the crosslinked networks. Radiation induced grafting of vinylic monomers (acrylic acid, methacrylic acid, acrylamide, *N*,*N*-dimethyl acrylamide and 1-vinyl-2 pyrrolidone) has been reported in literature. Homopolymerisation can be inhibited by adding various concentrations of Fe^{2+} or Cu^{2+} ions [20]. Radiation techniques, due to the additive-free initiation and easy processability, are very suitable tools for the synthesis of the hydrogels, used in biomedical applications which include wound dressings and local drug delivery in anticancer therapy [7,21]. Recently, Singh and Vashishtha [22] have modified the sterculia gum polysaccharide with 2-hydroxyethylmethacrylate (HEMA) and acrylic acid (AAc) by radiation induced crosslinking polymerization to develop the hydrogels meant for the drug delivery. The release of anti-diarrhea model drug ornidazole from the hydrogels occurred through non-Fickian diffusion mechanism.

Keeping in view, the pharmacological importance of psyllium polysaccharides and drug delivery devices based on hydrogels, psyllium, if suitably tailored to prepare the hydrogels, can act as the double potential candidates for the novel drug delivery systems. In our earlier studies, psyllium has been modified with vinyl monomers through chemical method by using *N*,*N*′-methylenebisacrylamide (*N*,*N*-MBAAm) as crosslinker and ammonium persulfate (APS) as initiator [3]. Therefore, the present study is an attempt, to synthesize psyllium-NVP based hydrogels by using radiation induced crosslinked polymerization and thereafter use these hydrogels as drug delivery devices. Polymeric networks have been characterized with SEMs, FTIR and swelling studies. Swelling behavior of the hydrogels has been studied as a function of monomer concentration in the hydrogels and temperature, pH and [NaCl] of the swelling medium. This paper discusses the swelling kinetics of the hydrogels and release dynamics of anticancer model drug 5-fluorouracil from the hydrogels to evaluate the swelling and drug release mechanism for the polymer matrix

2. Experimental

2.1. Materials and method

Plantago psyllium mucilage (Psy) was obtained from Sidpur Sat Isabgol factory (Gujarat, India), *N*-vinylpyrrolidone (NVP) was obtained from Acros organic, USA. 5-Fluorouracil was procured from Dabur India Ltd.

2.2. Synthesis of psy-cl-poly(NVP)

Reaction was carried out with 1 g psyllium husk and specific concentration of NVP taken in 10 mL of water in a test tube. The reaction mixture was irradiated with gamma rays of dose rate 2.43 kGy/h, in ^{60}Co gamma chamber for specific time. The crosslinking polymers thus formed were named as psy-*cl*-poly(NVP) hydrogels and were stirred in distilled water and ethanol for 1 h each to remove the soluble fraction left in this composite matrix and then were dried in an oven at 40 °C. On the basis of swelling of the hydrogels and surface consistency maintained by the hydrogels after 24 h swelling, the optimum reaction parameters were evaluated for the synthesis of psy-*cl*-poly(NVP) hydrogels by varying the monomer concentration from 1.88×10^{-1} mol/L to 9.40×10^{-1} mol/L and total radiation dose from 9.72 to 58.32 kGy,. The optimum concentration of NVP and radiation dose for the synthesis of hydrogels has been obtained 7.52×10^{-1} mol/L and 58.32 kGy, respectively. At the optimum reaction parameters, further polymers were synthesized and these