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The release dynamics of model drugs from the psyllium and *N*-hydroxymethylacrylamide based hydrogels

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Abstract

In order to utilize the psyllium husk, a medicinally important natural polysaccharide, for developing the novel hydrogels for the controlled drug delivery device, we have prepared psyllium and *N*-hydroxymethylacrylamide based polymeric networks by using *N*,*N*′-methylenebisacrylamide (*N*,*N*′-MBAAm) as crosslinker. The polymeric networks thus formed were characterized with scanning electron micrography (SEM), FTIR and thermogravimetric analysis (TGA) techniques to study various structural aspects of the networks and also with the swelling response of the polymeric networks as a function of time, temperature, pH and [NaCl]. Equilibrium swelling has been observed to depend on both structural aspects of the polymers and environmental factors. Maximum P_s 748.3 was observed at 13.0×10^{-3} mol/L of [*N*,*N*′-MBAAm] in 0.5 M NaOH solution. The release dynamics of model drugs (salicylic acid and tetracycline hydrochloride) from hydrogels has also been discussed, for the evaluation of the release mechanism and diffusion coefficients. The effect of pH on the release pattern of tetracycline has been studied by varying the pH of the release medium. In release medium of pH 7.4 buffer the release pattern of tetracycline drastically changes to the extent that mechanism of drug diffusion shifted from non-Fickian diffusion to Fickian diffusion. It has been observed that diffusion exponent '*n*' have 0.71, 0.67 and 0.52 values and gel characteristic constant '*k*' have 1.552×10^{-2}, 2.291×10^{-2} and 5.309×10^{-2} values in distilled water, pH 2.2 buffer and pH 7.4 buffer, respectively, for tetracycline release. In solution of pH 7.4 buffer, the rate of polymer chain relaxation was more as compare to the rate of drug diffusion from these hydrogels and it follows Fick's law of diffusion. The value of the initial diffusion coefficient for the release of tetracycline hydrochloride was higher than the value of late time diffusion coefficient in each release medium indicating that in the start, the diffusion of drug from the polymeric matrix was fast as compare to the latter stages.

Keywords: Drug delivery devices; Hydrogels; Psyllium; Release dynamics

1. Introduction

Recently, an increasing number of studies suggested the use of polysaccharide hydrogels as colon-specific drug delivery device. An example of the colonic delivery of drugs is the local delivery of salicylate derivatives for the topical treatment of ulcerative colitis and sometimes the local treatment of irritable bowel syndrome. Some recent examples include bypassing small intestine metabolism, achieving constant absorption rates for some molecules and delivering cationized antioxidant enzymes to the colonic epithelium (Rubinstein, 1995). The release rate of drugs from hydrogels was primarily determined by the swelling extent which further enhanced by addition of enzyme in buffer solutions (Chiu et al., 1999) whereas swelling was depended on composition of copolymer and pH of the surrounding medium (El-Hag Ali Said, 2005). The in vitro release of salicylic acid from the poly[bi(*o*-carboxyphenyl)adipate-polyethylene glycol] anhydrides polymers increased with the increase of polyethylene glycol content in the polymers, the increase of pH value of degradation buffer solution and the rat cecal contents in the release media (Cai et al., 2003, 2005).

A semi interpenetrating polymer networks (IPNs) of carboxymethyl cellulose and crosslinked poly(acrylic acid) have been prepared and their water-sorption capacity have been evaluated as a function of chemical architecture of the IPNs, pH, and temperature of the swelling medium (Bajpai and Mishra, 2004). The in vitro release studies of riboflavin, Vitamin B_{12} and Vitamin B_2 from pH-sensitive co-polymeric hydrogels were

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carried out at the physiological temperature 37 °C (Bajpai and Saxena, 2004; Bajpai and Dubey, 2004, 2005). The gels exhibit a sharp pH-dependent release behavior. With increasing concentration of cross-linker in the gel, the drug released was found to decrease. Moreover, with low content of cross-linker a nearly zero-order profile was obtained. The size of the cylindrical devices also affected the release kinetics and a linear dependency was observed between $t^{1/2}$ (i.e., the time required for 50% release) and the square of the diameter, thus supporting the Tanaka–Fillmore theory. The controlled release of active anti-microbial agents such as amoxicillin (Risbud and Bhonde, 2000), metronidazole (Portero et al., 2002), oxytetracycline (Mi et al., 1997) and tetracycline-HCl (Bittner et al., 1999) from the hydrogels have been studied and reported in literature.

Psyllium is the common name used for several members of the plant genus *Plantago* and its seeds have used commercially for the production of mucilage. The mucilage obtained from the seed coat by mechanical milling/grinding of the outer layer of the seeds and yield amounts to approximately 25% of the total seeds yield. Mucilage is (a white fibrous material) hydrophilic nature and forms the clear colorless mucilaginous gel by absorbing water. Gel-forming fraction of the alkali-extractable polysaccharides composed of arabinose, xylose and traces of other sugars (Fischer et al., 2004). Psyllium has been reported as a medicinally active natural polysaccharide. The cholesterol-lowering effect of psyllium has been reported in children (Davidson et al., 1996), as well as in adults (Oson et al., 1997). Psyllium supplementation has also improved blood sugar levels in some people with diabetes. The soluble fiber component of psyllium is believed to account for this effect (Anderson et al., 1999; Florholmen et al., 1982; Rodriguez-Moran et al., 1998). In a double-blind trial, people with ulcerative colitis had a reduction in symptoms such as bleeding and remained in remission longer when they took 20 g of ground psyllium seeds twice daily with water compared to the use of the medication mesalamine alone (Fernandez-Banares et al., 1999). Also, the combination of the two was slightly more effective than either alone. Psyllium has been reported to inhibit lactulose-induced colonic mass movements and to benefit patients with irritable bowel syndrome, improving both constipation and diarrhea (Washington et al., 1998).

Psyllium if suitably tailored to prepare the hydrogels, which can act as the potential candidates for novel drug delivery devices. The chemical modification of mucilage of *Plantago psyllium* (Psy), is not much reported. Some work on the grafting of polyacrylamide and polyacrylonitrile onto psyllium has been reported for the use in flocculation studies (Agarwal et al., 2002; Mishra et al., 2002, 2003, 2004a,b). Singh and coworkers have studied the metal ion sorption and swelling behavior of psyllium and acrylic acid based hydrogels (Singh et al., 2006). Therefore, the present study is an attempt, to synthesize psyllium and *N*-HMAAm based hydrogels, by using *N*,*N*′-MBAAm as crosslinker and ammonium persulfate (APS) as initiator; The polymeric networks [Psy-*cl*-poly(*N*-HMAAm)], thus formed were characterized by SEM, FTIR, TGA, and swelling response of the hydrogels were studied as a function of time, temperature, pH and [NaCl]. The release dynamics of model drugs (salicylic acid and tetracycline hydrochloride) from hydrogels have also been discussed, for the evaluation of the release mechanism and diffusion coefficients.

2. Experimental

2.1. Materials and method

P. psyllium mucilage (Psy) was obtained from Sidpur Sat Isabgol factory (Gujrat, India), *N*-hydroxymethylacrylamide (*N*-HMAAm) (Merck-Schuchardt, Germany), Ammonium persulphate (APS), Salicylic acid and *N*,*N*′-methylenebisacrylamide (*N*,*N*′-MBAAm) was obtained from S.D.Fine, Mumbai, India and were used as received. Tetracycline hydrochloride was obtained from the Ind-Swift Limited, Chandigarh, India.

2.2. Synthesis of Psy-cl-poly(N-HMAAm)

The optimum reaction parameters were evaluated for the synthesis of Psy-*cl*-poly(*N*-HMAAm) by varying [APS], [*N*-HMAAm] reaction time, amount of solvent from the morphology and swelling behavior of the polymeric networks (Table 1). Reaction carried out with 1 g of psyllium husk, 11×10^{-3} mol/L of APS, definite concentration of monomer and crosslinker in the aqueous reaction system at 65 °C temperature for 2 h. Polymers thus formed were stirred for 2 h in distilled water and for 2 h in ethanol to remove the soluble fraction and then were dried in air oven at 40 °C. At optimum reaction parameters different polymeric networks were synthesized by varying [*N*,*N*′-MBAAm] (from 6.45×10^{-3} to 32.40×10^{-3} mol/L) to study the effect of crosslinker variation on the structure of three dimensional networks and thereafter on the percent swelling of these polymeric networks. The polymer used for the study of release dynamics of model drugs was prepared with 15.0×10^{-3} mol/L of [*N*,*N*′-MBAAm] and 53.45×10^{-3} mol/L of [*N*-HMAAm].

2.3. Characterization

Psyllium and Psy-*cl*-poly(*N*-HMAAm) polymer were characterized by the following techniques.

2.3.1. Scanning electron micrography (SEM)

To investigate and compare the surface morphology of psyllium and Psy-*cl*-poly(*N*-HMAAm), SEMs were taken on Jeol Steroscan 150 Microscope.

2.3.2. Fourier transform infrared spectroscopy (FTIR)

FTIR spectra of psyllium and Psy-*cl*-poly(*N*-HMAAm) were recorded in KBr pellets on Perkin Elmer RXI FTIR SYSTEM to study the modified nature of psyllium.

2.3.3. Thermogravimetric analysis (TGA)

Thermo gravimetric analysis of psyllium and Psy-*cl*-poly(*N*-HMAAm) was carried out on a Schimatdzu Simultaneous Thermal Analyzer in air at a heating rate of 20 °C/min to examine the thermal properties of the polymers.