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Development of hydrogels by radiation induced polymerization for use in slow drug delivery

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HIGHLIGHTS

- Swelling of hydrogels decreased with increase in radiation dose.
- Swelling increased with increase in hydrophillicity of hydrogels.
- Slow release of indinavir from sulfated hydrogels.
- Drug release followed non-Fickian mechanism.

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ABSTRACT

In the present work, in order to improve the drug release profile of indinavir sulfate, a potent inhibitor of HIV protease, controlled drug delivery systems in the form of hydrogels have been designed by a radiation graft polymerization method. These hydrogels have been prepared by using dietary fiber psyllium and binary monomers mixture of acrylamide (AAm) and 2-acrylamido-2-methylpropanesulfonic acid (AMPSA). These polymers have been characterized with cryo-SEMs, FTIR, XRD and swelling studies. The swelling of hydrogels has been determined in solution of different pH, temperature and [NaCl]. in vitro release studies of model drug indinavir sulfate in different pH have been carried out to determine the drug release mechanism. The release of dug occurred through non-Fickian mechanism.

1. Introduction

Indinavir sulfate is a potent inhibitor of HIV protease which is widely used in the treatment of AIDS and prescribed in combination with other protease inhibitors, nucleoside analogs, or reverse transcriptase inhibitors (Deeks et al., 1997). It is rapidly absorbed following oral administration. Its narrow therapeutic window and poor systemic bioavailability create a risk of adverse effects. Hence, some slow drug delivery devices are required for its delivery. It has been reported that drug administration through polymer based drug delivery system improves its pharmacokinetics and pharmacodynamic profile (Chiappetta et al., 2009). It is a fact that AIDS had killed millions of people worldwide. Therefore, there is a great urgency to develop therapeutic agents and drug delivery systems to blunt the progress of pandemic AIDS.

Recently, polymeric hydrogels, specially based on polysaccharides, have attracted considerable attention as an excellent candidate for controlled release of therapeutic agents (Hoffman, 2012; Coviello et al., 2007). Hydrogels are three dimensional crosslinked polymer networks having hydrophilic properties and do not typically dissolve due to chemical or physical cross-links and/or chain entanglements. The equilibrium degree of swelling of pH-sensitive hydrogels is influenced by the charge of the ionic monomer, degree of ionization, concentration of ionizable monomer in the network and pH, ionic strength and composition of the swelling solution. In addition, other factors such as crosslinking density and hydrophillicity/hydrophobicity of the polymer also influence the degree of swelling (Klinger and Landfester, 2012; Qiu and Park, 2012; Li et al., 2006).

Hydrogels can be prepared by grafting of vinyl monomers and crosslinking of trunk polymers and/or grafted polymers onto polysaccharides. Radiation induced graft copolymerization reaction occurs by gamma radiation. Graft copolymerization of vinyl monomers from their binary mixtures has many advantages (Safrany et al., 2010, Rosiak et al., 1995). It incorporates different types of polymer chains containing various functional groups in the structure of backbone polymers. The condition of grafting reactions can be controlled and graft copolymer with desired properties may be obtained. Hence, this technique of graft copolymerization provides an opportunity to prepare tailor-made grafted chains of desired

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properties by using suitable monomers (El -Salmawi et al., 1997; Gupta and Khandekar, 2003; Coskun et al., 2005). The product formed by graft copolymerization of AAm and AAc onto the cellulose of wheat straw showed a water absorbency of 133.76 g/g in distilled water and 33.83 g/g in 0.9 wt% NaCl solution (Li et al., 2012). Yin et al. (2007) have synthesized the binary monomer based superporous hydrogels containing poly(AAc-co-AAm)/carboxymethyl chitosan IPN to enhance the mechanical strength, in vitro muco-adhesive force and loading capacity of hydrogels.

Psyllium polysaccharide is a gel-forming water-soluble fiber. The gel nature and composition of the polysaccharides extracted from the seeds of the *Plantago ovata* have been reported in the literature (Kennedy et al., 1979; Sandhu et al., 1981; Laidlaw and Purcival, 1950). It is highly branched arabinoxylan polysaccharide, a xylose backbone, and arabinose and xylose side chains. It has various pharmaceutical and food applications. Dietary fibers from psyllium have been used extensively both as pharmacological supplements and food ingredients. Psyllium has been reported for the treatment of diarrhea, constipation, irritable bowel syndrome, inflammatory bowel disease-ulcerative colitis, colon cancer, diabetes and hypercholesterolemia. Psyllium mucilage has been evaluated for its binding and disintegrating properties in tablet formulation and it showed comparable disintegration, hardness and release data as shown by starch (Marlett and Fischer, 2003 Saeedi et al., 2010; Shirsand et al., 2009; Tahir et al., 2010).

Keeping in view the gel forming nature of psyllium polysaccharide and radiation formation of hydrogels, in the present study an attempt has been made to develop the psyllium and binary monomer mixture of AAm and AMPSA based hydrogels by a radiation method meant for slow drug delivery applications. These hydrogels have been characterized by different physical techniques such as SEMs, FTIR, and XRD for the evaluation of structural aspects. The swelling kinetics of the hydrogels as a function of reaction parameters and, pH, temperature and NaCl concentration of the swelling medium have been studied for the evaluation of swelling mechanism and diffusion coefficients for the swelling of the hydrogels. in vitro release dynamics of model drug indinavir sulfate from the drug loaded hydrogels have been determined in different release mediums, for the evaluation of the release mechanism and diffusion coefficients.

2. Experimental

2.1. Materials and methods

Plantago psyllium mucilage was obtained from Sidhpur Sat Isabgol factory, Gujarat, India. 2-Acrylamido-2-methylpropane sulfonic acid (AMPSA) was obtained from Merck-Schuchardt, Germany. Acrylamide (AAm) was obtained from Sisco Research Laboratories, Mumbai, India. Indinavir sulfate drug was obtained from Cipla limited, Solan, Himachal Pradesh, India.

2.2. Synthesis of hydrogels

Synthesis of hydrogels was carried out by a radiation induced graft copolymerization method. The copolymerization was carried out in test tube with stoppers by mixing the psyllium with solution of both monomers (AAm and AMPSA) prepared in 10 ml distilled water. First, definite amount of both the monomers was dissolved in 10 ml water taken in test tube and then psyllium was added slowly with continuous stirring. The reaction system was irradiated in the ^{60}Co gamma chamber at a fixed total radiation dose in the presence of air in the solution in test tube. The crosslinked polymers formed after irradiation were stirred in 1:1 mixture of distilled water and ethanol for 2 h to remove the soluble fractions left in the polymers. These polymers were then dried in an oven at 40 °C till constant weight was obtained. These polymers were named as [psy-*cl*-poly(AAm-*co*-AMPSA)] hydrogels. 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(AAm-*co*-AMPSA) hydrogels by varying total radiation dose from 1.62 to 9.72 kGy, [AAm] from 1.41×10^{-1} to 7.05×10^{-1} mol/L (i.e. varied from 0.1 to 0.5 g of AAm in 10 mL water), [AMPSA] from 4.83×10^{-2} to 24.13×10^{-2} mol/L (i.e. varied from 0.1 to 0.5 g of AMPSA in 10 mL water). The optimum reaction parameters for further synthesis of hydrogels were obtained as total radiation dose=8.10 kGy, [AMPSA]=4.83×10^{-2} mol/L (0.1 g), and [AAm]=4.23×10^{-1} mol/L (0.3 g) (Table 1). The psy-*cl*-poly(AAm-*co*-AMPSA) hydrogels prepared at optimum reaction conditions were used for further studies such as swelling behavior of hydrogels in solution of different pH, salt and temperature and in vitro release dynamics of model drug indinavir sulfate from the drug loaded hydrogels. The dose rate was 1.62 kGy/h ($\pm$2%) and dose rate was measured by using a ceric-cerous dosimetry system. The samples were irradiated at the center of the gamma chamber-900 where dose rate was 1.62 kGy/h ($\pm$2%). The irradiation temperature was 25 °C. The grafting percentage of AAm and AMPSA onto psylllim was determined for the polymers prepared at optimum conditions. Grafting in the present study is graft yield and has been expressed as grafting percentage and was determined by using equation [Grafting %=(weight of the graft sample − weight of the trunk polymer/weight of the trunk polymer) × 100] (Table 1).

2.3. Characterization

The psy-*cl*-poly(AAm-*co*-AMPSA) polymers were characterized by cryo-scanning electron microscopy (cryo-SEM), energy dispersion analysis by X-rays (EDAX), Fourier transform infrared (FTIR) spectroscopy, thermogravimetric analysis (TGA) and X-Ray Diffraction (XRD) analysis. Cryo SEMs were taken on a Zeiss LEO 435 VP Microscope. Before the Cryo SEMs analysis, the samples were immersed in distilled water at 37 °C for 24 h. After this, the samples were immediately frozen by immersing in liquid nitrogen and were kept in it for 30 min. Thereafter, the frozen samples were

Table 1
Optimum reaction parameters for the synthesis of psy-*cl*-poly(AAm-*co*-AMPSA) hydrogels by the radiation method.

S. no.	Total radiation dose (kGy)	[AMPSA]		[AAm]		Psyllium (g)	Amount of water uptake after 24 h (g/g of gel)
		$\times10^2$ (mol/L)	(g)	$\times10^1$ (mol/L)	(g)		
1	1.62	4.83	0.1	7.05	0.5	1	21.71 ± 0.48
2	3.24	4.83	0.1	7.05	0.5	1	19.68 ± 0.95
3	4.86	4.83	0.1	7.05	0.5	1	19.63 ± 1.46
4	6.48	4.83	0.1	7.05	0.5	1	18.59 ± 1.33
5	8.10	4.83	0.1	7.05	0.5	1	17.17 ± 0.92
6	9.72	4.83	0.1	7.05	0.5	1	14.81 ± 0.68
7	8.10	4.83	0.1	7.05	0.5	1	17.17 ± 0.92
8	8.10	9.65	0.2	7.05	0.5	1	17.85 ± 0.83
9	8.10	14.48	0.3	7.05	0.5	1	19.56 ± 0.39
10	8.10	19.30	0.4	7.05	0.5	1	18.03 ± 0.48
11	8.10	24.13	0.5	7.05	0.5	1	Polymer was not formed
12	8.10	4.83	0.1	1.41	0.1	1	15.12 ± 0.81
13	8.10	4.83	0.1	2.82	0.2	1	15.80 ± 0.85
[a]14	8.10	4.83	0.1	4.23	0.3	1	17.81 ± 1.81
15	8.10	4.83	0.1	5.64	0.4	1	17.12 ± 0.53
16	8.10	4.83	0.1	7.05	0.5	1	17.17 ± 0.92

[a] Grafting=40%.