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Grafting of GMA and some comonomers onto chitosan for controlled release of diclofenac sodium

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ABSTRACT

In order to develop pH sensitive hydrogels for controlled drug release we have graft copolymerized glycidyl methacrylate (GMA) with comonomers acrylic acid, acrylamide and acrylonitrile, onto chitosan (Ch) by using potassium persulphate (KPS) as free radical initiator in aqueous solution. The optimum percent grafting for GMA was recorded for 1 g chitosan at [KPS] = 25.00×10^{-3} mol/L, [GMA] = 0.756×10^{-3} mol/L, reaction temperature = 60 °C and reaction time = 1 h in 20 mL H_2O. Binary monomers were grafted for five different concentrations at optimum grafting conditions evaluated for GMA alone onto chitosan. The graft copolymers were characterized by FTIR, XRD, TGA and SEM. The swelling properties of chitosan and graft copolymers were investigated at different pH to define their end uses in sustained release of an anti-inflammatory drug, diclofenac sodium. Percent drug release w.r.t. drug loaded in polymeric sample was studied as function of time in buffer solutions of pH 2.0 and 7.4. In vitro release data was analyzed using Fick's Law. Chitosan grafted with binary monomers, GMA-*co*-AAm and GMA-*co*-AN showed very good results for sustained release of drug at 7.4 pH.

1. Introduction

Graft copolymerization is a suitable and convenient technique to modify natural polymers. Modification of biopolymers by grafting has been extensively studied yet newer dimensions of applications of these polymers are attracting attention of the researchers. Chitosan is one such abundantly found biopolymer [1] on earth after cellulose. Chitosan is obtained by the alkaline deacetylation of chitin [2]. For a breakthrough in its utilization in frontline technologies, graft copolymerization onto chitosan enlarges its spectrum of its applications by choosing various types of side chains. Both hydroxyl and amino groups on chitosan are possible sites for incorporating desired functional groups by grafting [3]. Literature survey reveals that recently a good amount of work has been carried out on grafting of various vinyl monomers onto chitosan and its derivatives using different initiating systems like ceric ammonium nitrate [4,5], potassium persulfate [6,7] ammonium persulfate [8], azobisisobutronitrile [9] and using potassium bromate/silver nitrate redox pair [10]. Grafting of polyacrylamide using microwave irradiation [11] and butyl acrylate in acetic acid aqueous solution using gamma radiations [12] was also reported onto chitosan. Chitosan based sensitive hydrogels were fabricated by combination with polymers such as poly methacrylic acid [13], poly acrylic acid [14], poly N-isopropylacrylamide [15,16], poly acrylonitrile [17], poly acrylamide [18], glycidyl methacrylate [19]. Recently, chitosan based hydrogels sensitive to external stimuli such as temperature [20], pH [21] and electric currents [22] are receiving much attention as drug delivery devices. Chitosan and its derivatives are reported in literature for control release of variety of drugs like diclofenac sodium [23], amoxicillin [24], bovine serum albumin [25], clozapine [26] and 5-Fluorouracil [27]. pH-sensitive interpenetrating polymeric network microgels based on chitosan reported for controlled released of cefadroxil [28] and acyclovir [29] drugs. Cumulative release characteristics of semi-interpenetrating networks of N,N′-dimethylacrylamide and chitosan for chlorothiazide, anti-hypertensive drug, were investigated in pH 1.2 and 7.4 media [30]. Chitosan blended with different amounts of polycaprolactone used for control delivery of ofloxacin [31].

Chitosan because of biocompatibility, biodegradability and non toxic properties has led to development of new drug delivery system [32]. In the present work, we have synthesized pH sensitive graft copolymers of chitosan with binary vinyl monomers by free radical initiation. Chitosan and graft copolymers were studied as

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support for sustained release of diclofenac sodium (DS), an anti-inflammatory drug at gastrointestinal pH.

2. Experimental

2.1. Materials

Chitosan (Sisco Research Laboratories Pvt. Ltd., Mumbai, India), GMA (Sisco Research Laboratories Pvt. Ltd., Mumbai, India), acrylic acid (AAc) (Merck, Germany), acrylamide (AAm) (Merck, Germany), acrylonitrile (AN) (S.D. Fine, India) and potassium persulphate (Ranbaxy, SAS Nagar, India) were used as received. All the chemicals used were of analytical grade.

2.2. Graft copolymerization

The optimum grafting reaction conditions for grafting of GMA onto 1 g of chitosan were obtained by free radical mechanism using KPS. The grafting reaction scheme was designed as one parameter was varied for a set of reaction keeping other reaction parameters constant (Table 1). The parameter which gave the maximum percent grafting (P_g) was selected for next step. Grafting onto chitosan was performed with known amount of monomer and initiator at 60 °C for 1 h in different solvents. The solvent in which maximum P_g was observed was selected and then effect of amount of solvent was studied. After optimizing amount of solvent, concentration of initiator was changed to have maximum P_g and then effect of change in concentration of monomer was studied. Finally reaction time and temperature were optimized to get optimum reaction conditions for grafting of GMA. At optimum grafting reaction conditions grafting of binary monomer mixtures of GMA with some comonomers (CM) as AAc, AAm and AN was carried over five concentrations of the comonomers.

2.3. Separation of homopolymers/copolymers

Graft copolymers and homopolymer were separated by solvent extraction method using ethyl methyl ketone (EMK) as solvent for poly(GMA). Extraction was carried until constant weight of graft copolymer was obtained. Copolymers or any amount of homopolymer of GMA or comonomers was removed by using different solvent systems of equal solvent compositions viz.: EMK – water for poly(GMA-*co*-AAc), poly(GMA-*co*-AAm), poly(AAc) and poly(AAm) and EMK – DMF for removal of poly(MMA-*co*-AN) and poly(AN) from the graft copolymers. The percent grafting (P_g) and percent grafting efficiency (%*GE*) were calculated which can be expressed as [33]:

$$P_g = \frac{W_1 - W_0}{W_0} \times 100$$

$$\%GE = \frac{W_1 - W_0}{W_2} \times 100$$

where W_0 is weight of polymer backbone, W_1 is weight of graft copolymer and W_2 is weight of monomer charged.

2.4. Characterization of graft copolymers

Characterization of chitosan and its graft copolymers were done by FTIR, XRD, SEM, thermal analysis and swelling studies. FTIR spectra of chitosan and its graft copolymers were recorded using Thermo Nicolet (Model 6700) spectrometer in KBr pellets. Scanning Electron Micrographs were taken on Jeol, JSM-6100 at an accelerating voltage of 20 kV. X-ray Diffraction studies were carried out using X'Pert PRO (PAN analytical, Netherlands), Rigaku Rota Flex operating with Cu Kα radiation, 45 kV, 40 mA and equipped with a graphite monochromator. Thermal analysis was done on Shimadzu DTG-60; simultaneous TG/DT model. Swelling studies were carried out on chitosan and graft copolymers at different pH. 25 mg of the copolymer was taken in 10.00 mL of water. Surface water on the swollen polymer was removed by softly pressing between the folds of filter paper and increase in weight was recorded. Percent swelling (P_s) was calculated by the following expression [34].

$$P_s = \frac{W_s - W_d}{W_d} \times 100$$

where W_s is weight of swollen polymer and W_d weight of dried polymer.

2.5. Drug release

Sorption of diclofenac sodium (DS) has been studied by equilibration method on graft copolymers of chitosan. Chitosan and its graft copolymers with maximum P_g were studied for DS drug release behaviour at variable conditions of pH. All readings of drug solution were taken at 276 nm at Thermo Evolution 300 model UV–vis spectrophotometer. A standard curve was prepared of drug solution by plotting graph between absorption values and concentration of drug solution by varying the concentration of drug solution from 2 μg/mL to 100 μg/mL. 25 mg of polymeric samples were dipped in 10 mL solution of concentration 100 μg/mL for 24 h. Drug uptake was calculated by taking absorption values of the filtrate. Then drug loaded polymeric samples were put in 10 mL buffer solution of pH 2.0 and 7.4 to study the release pattern after regular interval of time. Values of concentration of drug release were calculated from corresponding absorption values of drug solution by using *Mathematica 7* software from standard curve. Buffer solution of pH 2.0 was prepared by mixing 50 mL of 0.2 M KCl and 7.8 mL of 0.2 M HCl. Another buffer solution of pH 7.4 was prepared by mixing 100 mL of 0.1 M KH_2PO_4 and 78.2 mL of 0.1 M NaOH.

3. Results and discussion

Effects of various reaction parameters on P_g and %*GE* of GMA onto chitosan have been investigated and results are discussed.

3.1. Effect of nature and amount of solvent system

Solvent interacts not only with the backbone polymer but also with initiator system and monomer and such interactions are important factor that determines graft yield. In the present study, effects of solvents such as acetone, benzene, dioxane, MeOH and water on P_g and %*GE* were studied in 10.00 mL of these solvents keeping other reaction conditions constant. The order of P_g in these solvents can be presented as acetone < dioxane < benzene < carbon tetrachloride < water (Table 1). Maximum P_g (45.5) as well as %*GE* (42.33) was observed in water. Solubilization requirements of the initiator play important role to increase grafting. KPS easily undergo dissociation in water to give $SO_4^{\bullet -}$ radicals which generate radical sites on backbone and monomeric units for graft copolymerization. But KPS is not soluble in organic solvents thus lower P_g and %*GE* was observed in these solvents.

Amount of water was varied in the range 05.00 mL to 25.00 mL and appreciable changes in the graft yield have been observed. The optimum value of P_g (77.7) and %*GE* (72.28) were reported at 20.00 mL water (Table 1). With higher dilution of reaction system results in decrease in P_g and %*GE* as accessibility of reacting species to both monomer and backbone polymer was diminished and enhances the chances of homopolymer formation.