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pH responsive graft copolymers of chitosan

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ABSTRACT

Grafting suitable polymers onto chitosan can produce cationic or polyampholyte polymers or hydrogels that are potential smart biomedical materials. Chitosan-*graft*-[poly(diethylamino)ethyl methacrylate] has been prepared in three different physical forms as linear free chains in solution, chemical gels crosslinked with glutaraldehyde, and poly(diethylamino)ethyl methacrylate] grafted onto chitosan tripolyphosphate gel beads. In addition to chemical structure, the graft copolymers were characterized with respect to their dissolution and swelling behavior in aqueous solution. It has been established that solubility of the products is controlled by the grafting yield. While pH sensitive polymers, which collapse at a given pH value are obtained at lower grafting yields, hydrogels form at higher grafting yields with pH responsive swelling behavior. Glutaraldehyde crosslinked chitosan-*graft*-[poly(diethylamino)ethyl methacrylate] gels and chitosan tripolyphosphate gel beads grafted with poly[(diethylamino)ethyl methacrylate] exhibit pH sensitive swelling with highest equilibrium swelling capacity at pH = 1.2.
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1. Introduction

Polymers that are classified as pH responsive materials contain ionizable groups, which respond to the pH of the environment. A polymer containing basic groups such as amine ($-NH_2$), imidazole or pyridine group becomes protonated at low pH in which the H^+ ion concentration is high and hence is solubilized. At high pH, it becomes neutralized and undergoes a transition to the collapsed state or precipitates out of solution. Hence a phase change is observed. A polymer containing acidic groups such as carboxylic acid group obeys the same principle but behaves in the opposite way to a basic polymer. It exists in solution under basic conditions and collapses in acidic medium. pH responsive hydrogels, on the other hand, respond to pH changes by undergoing volume transition according to the pH of the environment.

Polymers and hydrogels with pH responsiveness are drawing increasing attention especially for targeted drug delivery as the pH of the tissues and cells show variations depending on their type and function. For example, in the GI tract pH of the stomach is 1.0–3.0, pH of the duodenum is 4.8–8.2, the pH of the colon is 7.0–7.5 [1]. Furthermore, lysosomes inside the cells have a pH around 5.0. In some cases, pH of tumor cells may change between 5.7 and 7.8 [2]. These properties can be used to induce pH sensitive drug delivery [1–3].

Chitosan is a biobased polymer derived from the natural polymer chitin which is a polysaccharide of β (1 → 4) linked *N*-acetylglucose units shown in Fig. 1(a). Chitosan is the partially deacetylated form of chitin. It is a copolymer of β (1 → 4) linked *N*-acetylglucose units and β (1 → 4) linked glucosamine units as illustrated in Fig. 1(b). Degree of deacetylation (DD) is one critical characteristic of chitosan, which affects its physicochemical responses and biological activity.

The importance of these polymers for biomedical applications comes primarily from their biodegradability, biocompatibility and relative non toxicity. Their versatility in terms of chemical and physicochemical properties add to their value. They are polyfunctional polymers with ease of modification, chelation/complexation capability, and ability to form chemically and physically crosslinked networks leading to gels, films, fibers, microspheres and nanospheres. They are biologically active polymers bearing mucoadhesivity, antibacterial activity, hypocholesterolemic activity in addition to acting as permeation enhancer, wound healing accelerator, having stimulatory effects on immune cells and local cell proliferation and integration of the implanted material with the host tissue [4].

Grafting is one polymer modification technique in which a polymer is linked to the backbone of a parent polymer, the substrate, by chemical linkages. It is a preferred method of polymer modification for biomedical applications for several reasons. It allows surface modification, as well as alteration of the bulk properties [5,6]. Furthermore, the shape and morphology of the polymer chain is known to affect the biological responses produced. As graft copolymers

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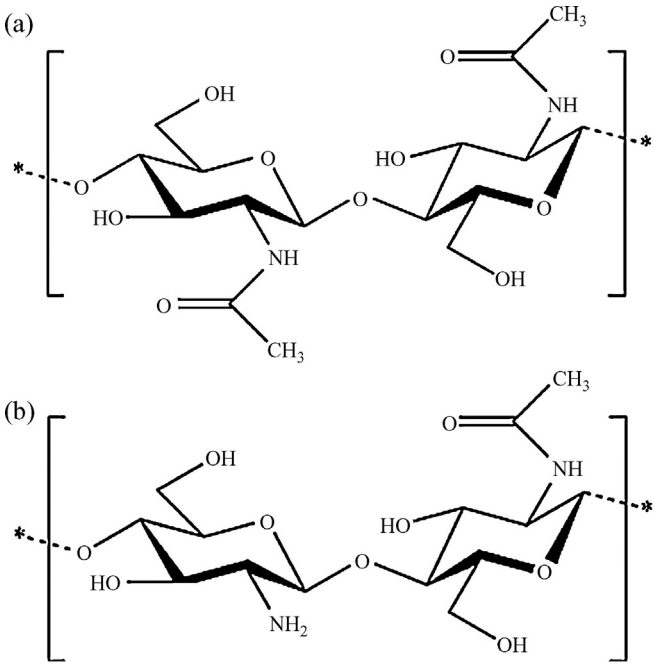

Fig. 1. Chemical structure of (a) chitin and (b) chitosan.

are branched polymers they exhibit different mechanical properties, and solution properties than their linear counterparts offering diversity in choices for given applications [6].

Chitosan was demonstrated to be a suitable substrate for graft copolymerization of synthetic polymers for pH sensitive polymer and hydrogel design as it is a multi functional polymer with one primary alcohol on C-6, one secondary alcohol on C-3, and one amine or acetamide on C-2. It is soluble in aqueous acid solutions; a suitable medium for redox initiation. Grafting suitable polymers onto chitosan can produce cationic or polyampholyte polymers as potential drug delivery or controlled release agents. This has been thoroughly studied using redox initiation [7–19]. Less frequent examples of photo or radiation induced grafting are also available [20–27]. Newer strategies such as ATRP, RAFT and/or click chemistry gave graft copolymers of chitosan with well-defined architecture [28,29,20]. Cerium(IV) ammonium nitrate (CAN) and potassium persulphate (KPS) or ammonium per sulphate (APS) are commonly used to initiate grafting onto chitosan. Generally accepted mechanisms [30] that proceed either via direct oxidation or complex formation are illustrated in Fig. 2(a)–(c). Similar mechanisms to those of Ce^{4+} initiated mechanism have been proposed for grafting onto chitosan by potassium per sulphate initiation [8,31]. It is clear that the possibility of obtaining a mixture of products is always available independent of the type of the initiator used. However, cleaner products are obtained as potassium salt is water soluble and there is no complex formation mechanism involved as in the case of Ce^{4+} initiation. One characteristic of grafting onto chitosan by redox initiation is chain scission as a result of oxidation [31]. According to our observations, in some cases depending on the type, an electron donating monomers such as 4-vinyl pyridine, and concentration of the monomer, and the pH of the medium the chitosan-Ce^{4+} complex formed does not dissociate completely [7]. Usually a yellow colored product is obtained which is insoluble in common solvents. Hence products contaminated with Ce^{4+} are obtained which is a serious drawback for biomedical applications.

This article describes graft copolymerization of (2-diethylamino) ethylmethacrylate), DEAEM (Fig. 3), onto chitosan under homogeneous and heterogeneous conditions using potassium persulphate initiator. Chitosan-*graft*-poly((2-diethylamino) ethylmethacrylate) has been prepared in three different physical forms as linear free chains in solution, chemical gels crosslinked with glutaraldehyde, and by grafting poly((2-diethylamino) ethylmethacrylate) onto chitosan tripolyphosphate gel beads to explore the limits of chitosan/DEAEM/KPS grafting system. The chemical structure has been characterized by FTIR and NMR spectroscopies. The effect of the grafting yield, the chemical structure and the physical form on the pH responsive swelling and dissolution behavior has been investigated.

2. Materials and methods

2.1. Materials

Chitosan (CHI, medium molecular weight, Aldrich, Germany, molar mass 4.0×10^5 g/mol, and degree of deacetylation of 85%), 2-diethyl amino)ethyl methacrylate (DEAEM, Aldrich, Germany), Glutaraldehyde (GA, Aldrich, Germany), potassium persulfate (KPS, Aldrich, Germany), acetic acid (Riedel-de Häen, Germany), ethanol (Riedel-de Häen, Germany), acetone (Riedel-de Häen, Germany), pentasodium tripolyphosphate (TPP), 1,2-dichloroethane (Sigma-Aldrich, Germany) were used without any further purification.

2.2. Preparation of CHI-graft-PDEAEM under homogeneous conditions

A 25 mL sample of CHI solution of concentration 1% (w/v) prepared in 1% (v/v) acetic acid solution was placed in a two-neck reaction vessel. A required amount of KPS, and monomer (2-diethylamino)ethyl methacrylate, DEAEM, were then added into CHI solution respectively under nitrogen atmosphere and at 70 °C. The reaction was carried out for 4 h under vigorous magnetic stirring at 1200 rpm. Then, the product was precipitated in acetone and was dried at 50 °C overnight. Preparation conditions of all CHI-*graft*-PDEAEM prepared under homogeneous conditions are given in Table 1. The products were dialyzed against distilled water for 24 h using a dialysis membrane of 6000–8000 MWCO to remove any unreacted monomer, initiator or any oligomers that may have been formed. After dialysis the products were cleaned by soxhlet extraction using 1,2-dichloroethane as the solvent to obtain pure graft copolymers free from any homopolymer.

2.3. Preparation of GA crosslinked CHI-graft-PDEAEM gels

The gelation time for CHI and CHI-*graft*-PDEAEM samples dissolved in acetic acid (pH = 3.0) and pH = 1.0 (HCl/KCl buffer) was measured by placing 4.0 mL solution in a glass test tube. The

Table 1
Preparation conditions of all CHI-*graft*-PDEAEM.

Sample ID	DEAEM (mL)	*T* (°C)	Time (h)	KPS (g)	H%	G%
CHI-*graft*-PDEAEM(294)	0.25	70	4	0.1250	3.37	294
CHI-*graft*-PDEAEM(361)	0.50	70	4	0.1250	4.95	361
CHI-*graft*-PDEAEM(356)	0.75	70	4	0.1250	3.26	356
CHI-*graft*-PDEAEM(221)	1.00	70	4	0.1250	1.69	221

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