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## Chemical Modification of Sodium Hyaluronate via Graft Copolymerization of Acrylic Acid Using Ammonium Persulfate

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### ABSTRACT

The polysaccharide, sodium hyaluronate, was modified using ammonium persulfate-initiated graft copolymerization of acrylic acid under inert atmosphere in a homogeneous aqueous medium. Grafting was confirmed using gravimetrically method and solubility test. The effect of various factors affecting on grafting, i.e. concentration of the initiator, monomer, and polysaccharide as well as the reaction temperature were studied by conventional methods to achieve the optimum grafting parameters. According to the empirical rates of the polymerization and the graft copolymerization of acrylic acid onto sodium hyaluronate backbone, the overall activation energy of the graft copolymerization reaction was estimated to be 16.7 kJ/mol.

**Keywords:** sodium hyaluronate, acrylic acid, graft copolymerization, ammonium persulfate.

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## INTRODUCTION

Considerable interest has been focused on chemical modification by free radical graft copolymerization of hydrophilic and hydrophobic vinyl monomers biopolymers such as polysaccharides [1-3]. These biodegradable and low cost graft copolymers, with new properties, can be used in many applications such as textiles, paper industry, agriculture, medical treatment and also in petroleum industry as flocculants and thickening agents [4, 5].

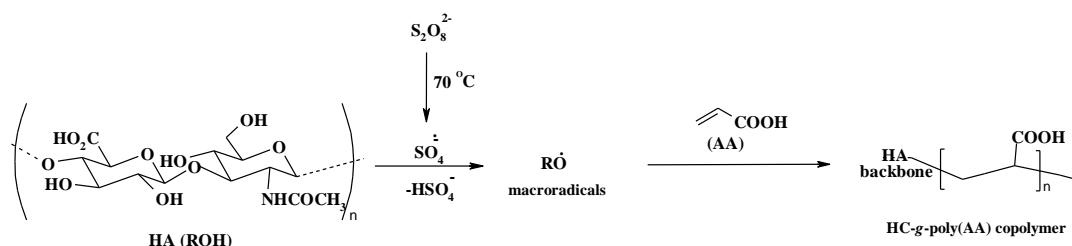
Graft copolymers are prepared by first generating free radicals on the polysaccharide backbone and then allowing these radicals to serve as macroinitiators for the vinyl monomers. Graft copolymerization can be carried out with different initiator systems. Among them, potassium persulfate, ammonium persulfate, benzoyl peroxide, azo bisisobutyronitrile, and ceric ammonium nitrate are widely used for the synthesis of graft copolymers [6, 7].

The present report describes graft copolymerization of acrylic acid onto sodium hyaluronate backbone, initiated by ammonium persulfate.

## Results and Discussion

### Graft copolymerization mechanism

The mechanism of grafting acrylic acid onto sodium hyaluronate using ammonium persulfate as a water soluble oxidizing initiator is shown in the Scheme 1. The persulfate initiator is decomposed under heating to generate sulfate anion-radical. The radical abstracts hydrogen from the hydroxyl group of the polysaccharide to form alkoxy radicals on the substrate. So, this persulfate-saccharide redox system is resulted in active centers on the substrate to radically initiate polymerization of acrylic acid led to a graft copolymer.



**Scheme 1.** A brief proposed mechanism for APS-induced grafting of poly(AA) onto HA.

### Proof of grafting

Evidence of grafting was obtained by gravimetrically method as well as solubility characteristics of the products.

The existence of poly(AA) grafting was confirmed by the difference between solubility of the graft copolymer and the non-grafted homopolymer. Sodium hyaluronate and poly(AA) are soluble in water and DMF, respectively. When a reaction product was extracted with DMF and alternatively with water for 24 h, an insoluble solid still remained. A

physical mixture of sodium hyaluronate and poly(AA) was treated in the same way and was found to dissolve completely. Therefore, it is obvious that the resulted graft copolymer was not a simple physical mixture, but some chemical bonds must exist between the sodium hyaluronate substrate and poly(AA) macromolecules.

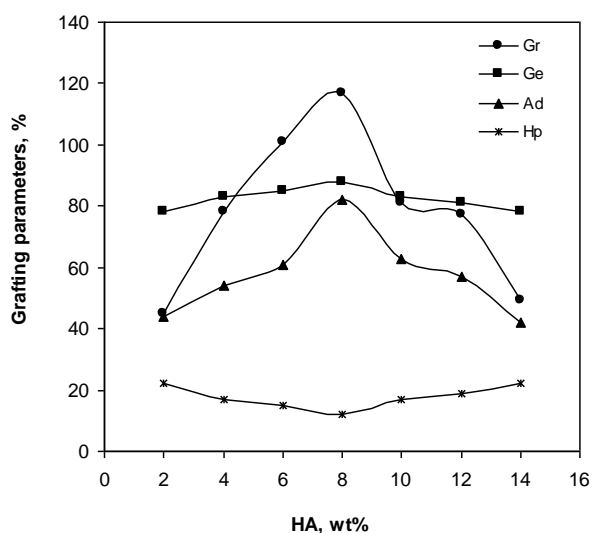
The existence of poly(AA) grafting was also monitored gravimetrically. Increase in the mass of sodium hyaluronate, after extraction of homopolymer, was taken as evidence for grafting. This weight gain in sodium hyaluronate forms the basis for the determination of the grafting parameters.

### Effect of reaction conditions on grafting

To optimize the reaction conditions, the effect of concentration of acrylic acid, sodium hyaluronate, and ammonium persulfate as well as grafting temperature was studied in the light of grafting parameters.

#### *Effect of polysaccharide concentration*

Figure 1 presents the relationship between sodium hyaluronate concentration and the grafting parameters. The increase in the sodium hyaluronate amount from 2 to 8 wt% brings about enhancement in grafting, whereas further increase in the substrate decreases the grafting. The initial increase may be due to the availability of more grafting sites, where polysaccharide can be grafted. Subsequent decrease in grafting parameters can be explained on the basis of increase in viscosity of the medium, which hinders the movement of free radicals.



**Figure 1.** Effect of polysaccharide concentration on the grafting parameters.

#### *Effect of initiator concentration*

Graft copolymerization was studied at various initiator concentrations by keeping other reaction conditions constant. As shown in Figure 2, the %Ge and %Gr increase with increasing in the initiator concentration and reach at a maximum value. Further increase of concentration of APS beyond 0.009 mol/L disfavoured the grafting parameters. A relatively

high concentration of the initiator may cause a reduction of %Ge and %Gr due to increase in the number of sodium hyaluronate free radicals terminated prior to AA addition. Furthermore, homopolymer formation at higher APS concentrations which compete with the grafting reaction for available monomer could lead to decrease in the %Ge and %Gr.

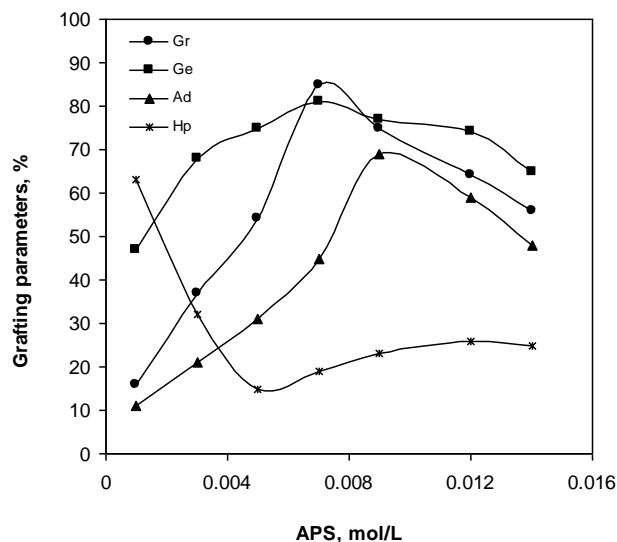


Figure 2. Grafting parameters as functions of initiator concentration.

*Effect of monomer concentration*

The effect of AA concentration on the grafting parameters is presented in Figure 3. In the initial stages, though both %Ge and %Gr rise with increase in AA concentration, but beyond certain concentration of monomer, 0.7 mol/L, the grafting parameters decrease. The initial increase in grafting parameters could be associated with the greater availability of monomer molecules in the vicinity of sodium hyaluronate macroradicals. The decrease of %Gr and %Ge with further increase in the AA concentration may be explained as follows: (a) preferential homopolymerization Hp over graft copolymerization, (b) increasing the viscosity of reaction medium, which hinders the movement of free radicals, and (c) increase in the chance of chain transfer to monomer molecules.

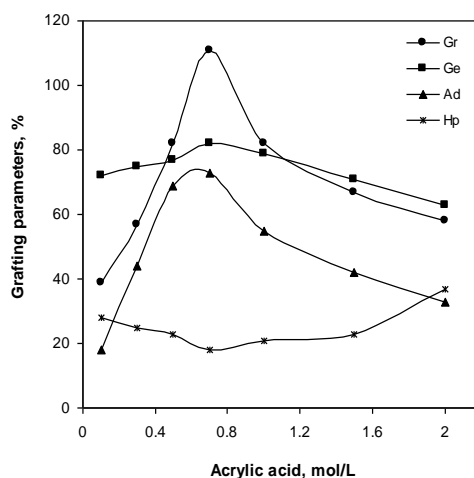
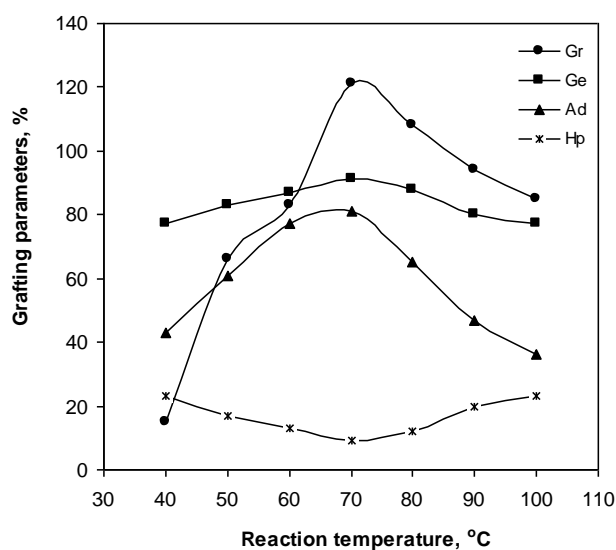


Figure 3. Effect of the monomer concentration on the grafting parameters.

### Effect of reaction temperature

Figure 4 shows the influence of reaction temperature on grafting. An increase in temperature upto 70 °C increases the grafting parameters. This behaviour may be due to the higher rate of diffusion of acrylic acid molecules to polysaccharide macroradicals. Moreover, higher temperatures increase the solubility of the reactants. On the other hands, since APS is a thermally dissociating initiator, it reacted very slowly at temperatures lower than its dissociation temperature 70 °C. The lower initiating radicals limited the extent of polymerization. The subsequent lower grafting can be explained on the basis of (a) oxidative degradation of polysaccharide chains by sulfate radical-anions and (b) increasing rate of termination and chain transfer reactions.



**Figure 4.** Effect of the reaction temperature on the grafting parameters.

Using the following empirical formula, the rate of graft copolymerization ( $R_g$ ) was calculated:

$$R_g (\text{mol} \cdot \text{s}^{-1} \cdot \text{m}^{-3}) = \frac{\text{Weight of grafted polymer}}{\text{Molecular weight of monomer} \cdot [\text{reaction time (s)}] \cdot \text{volume (m}^3\text{)}}$$

The overall activation energy ( $E_a$ ) of the graft polymerization reaction was calculated by using of the above equation and the slope of the plot  $\ln R_g$  versus  $1/T$  based on Arrhenius relationship [ $k_p = A \exp(-E_a/RT)$ ]. Therefore,  $E_a$  for the graft copolymerization was found to be 16.7 kJ/mole.

## EXPERIMENTAL

### Grafting procedure

Graft copolymerization of acrylic acid onto sodium hyaluronate was carried out with APS radical initiator under argon atmosphere. In a 100 mL flask, certain amount of sodium hyaluronate (0.5-3.0 g) was dissolved in 50 mL of degassed distilled water. The flask was

placed in a water bath with desired temperature (40-100 °C). A given amount of monomer, AA (1.5-5.0 g), was added to the flask and the mixture was stirred for 15 min. Then, the initiator (0.02-0.50 g) was added to the mixture and continuously stirred for 120 min. An inert gas (argon) was gently bubbled into the reactor to remove the oxygen during the graft copolymerization reaction. The product was then worked up with methanol (200 mL) and dried in oven at 50 °C for 5 h.

### Evaluation of grafting parameters

The grafting parameters used to characterize the nature of the copolymer are defined with the weight basis expressions as reported by Fanta [4]. The percentage of grafting ratio (Gr%) stands for the weight percent of the graft copolymer synthetic part (PAA grafted) formed from initial sodium hyaluronate used.

$$\text{Grafting ratio}(\%Gr) = \frac{\text{Weight of grafted polymer}}{\text{Weight of substrate}} \cdot 100$$

The percentage of grafting efficiency (Ge%) stands for the grafted PAA formed from initial monomer charged.

$$\text{Grafting efficiency}(\%Ge) = \frac{\text{Weight of grafted polymer}}{\text{Weight of polymer formed}} \cdot 100$$

The percentage of Add-on (Ad%) is the weight percent of the grafted PAA of the graft copolymer.

$$\text{Add on}(\%Ad) = \frac{\text{Weight of grafted polymer}}{\text{Weight of graft copolymer}} \cdot 100$$

The percentage of homopolymer (%Hp) denotes the weight percent of the homopolymer formed from initial monomer charged.

$$\text{Homopolymer}(\%Hp) = 100 - \%Ge$$

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