글라이콜 키토산의 위치선택적 아실화

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Regioselective Acylation on Glycol Chitosan

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1. Introduction

Chitin is a natural biopolymer that, with its derivative chitosan, has been represented as a biomaterial with considerable potential in wide ranging medical applications.
But there are some limitations in using chitosan as attained, for instance, the problem of water solubility[1]. In order to use chitosan in various applications (e.g. drug carrier), chemical modifications are often necessary[2]. Among the chemical modifications, acylation is one of the easiest and the most effective methods to obtain the water solubility[3] and the novel functionality in chitosan[4] which can be used for conjugation of drug, etc.

The acylation of chitosan has been carried out in many researches as a preliminary step[5], to the conjugation of drug, etc. However, little attention has been paid to the details of acylation reaction itself. For example, up to now, the degree of acylation as a function of the molar ratios of reactants was mostly investigated,[6,7] despite the possibility that the regioselective acylation may regulate the behavior of further chemical conjugation[8], e.g. drug loading etc.. So We tried to clarify the acylation behavior from a different standpoint, with not only the degree of acylation but also the regioselectiveness. In this study, using glycol chitosan instead of chitosan to obtain the water solubility, we acylated with varying the molar ratio of succinic anhydride, methanol content of solvent, and the reaction temperature which could control the acylation behaviors.

2. Experimental

2.1. Materials

Glycol chitosan (85.6%, Sigma Chemical Co., Japan) was purified with methanol three times and dried in vacuo. Succinic anhydride (TU, Aldrich Chemical Co., U.S.A.) and methanol (anhydrous, Mallinckrodt Baker Inc., U.S.A.) were used without further purification.

2.2. Experiments

Glycol chitosan (0.2g) was dissolved in 10 mL distilled water, and succinic anhydride was dissolved in 10 mL methanol, respectively. Before mixing two solutions, methanol was added into glycol chitosan/water solution and stirred for 1 hour. The mixture solution were stirred for 24 hours, and dialyzed for 2 days, and freeze-dried.

2.3. Measurements

Infrared spectra of the samples were obtained on PerkinElmer, spectrum GX FT-IR Spectrometer with KBr pellet method. ^{1}H-NMR spectra were recorded on Bruker, Avance 500 MHz

spectrometer. D_2O was used as a solvent. Elemental analysis was performed with EA1110(CE Instrument, Italy)

3. Results and Discussion

3.1 The effect of the molar ratio of acylating agent

As presumed, the more amount of succinic anhydride was used, the more hydroxyl groups were acylated. However, it was found that the lower molar ratio was favorable to the selective N-acylation. Fig.1. shows selectively N-acylated and N,O-acylated NMR spectra of succinylated glycol chitosan.

3.2 The effect of MeOH content in the solvent

MeOH content which is known to be effective for selective N-acylation[9] was controlled for regioselective acylation. It was found that in the specific amount of MeOH contents in the solvent, the gelation occured due to high degree of O-acylation, which means acylation site could be controlled by the regulation of MeOH content. Fig.2. shows NMR spectra of succinylated chitosan gel and water soluble glycol chitosan.

4. Conclusions

In the acylation on the glycol chitosan, MeOH content in the solvent was an important factor regulating the acylating site. And also the molar ratio of acylating reagent could be used for the regioselective acylation on glycol chitosan.

5. References

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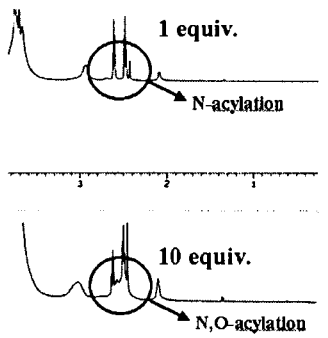

Fig.1. The comparison of NMR spectra between selectively N-acylated glycol chitosan and N,O-acylated glycol chitosan

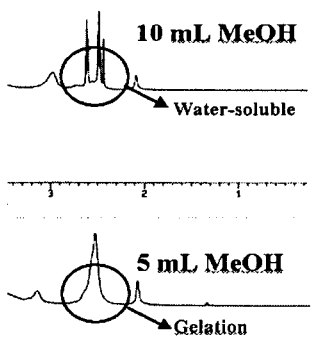

Fig.2. The comparison of NMR spectra between water soluble glycol chitosan and succinylated glycol chitosan gel