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Enhancing mucoadhesive properties of chitosan with methacryloyl and crotonoyl groups.

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SUMMARY

Nasal drug delivery holds promise for targeted administration to the brain. Mucoadhesive polymers are crucial for prolonging drug retention in the nasal mucosa. This study focuses on synthesizing and characterizing novel derivatives by reacting chitosan with crotonic and methacrylic anhydrides. The structure of the resulting derivatives was confirmed through ^{1}H NMR and FTIR spectroscopies, while turbidity measurements revealed pH-dependent solubility profiles. Spray-drying chitosan solutions with sodium fluorescein enabled flow-through studies and texture analysis, demonstrating improved retention on sheep nasal mucosa. The findings emphasize the potential of tailored chitosan modifications for enhancing nasal drug delivery.

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INTRODUCTION

Nasal drug delivery has emerged as a highly promising and non-invasive approach for targeted drug administration to the brain, offering a potential solution for treating neurodegenerative diseases such as Alzheimer's and Parkinson's. Currently available therapeutic interventions for these conditions focus primarily on providing symptomatic relief but are often associated with systemic side effects due to the limited ability of drugs to effectively penetrate the blood-brain barrier (BBB). To overcome this challenge, our study delved into the modification of chitosan, a mucoadhesive polymer, by incorporating unsaturated groups through the reactions of this polysaccharide with methacrylic (MA) and crotonic anhydrides (CA). These unsaturated groups can form covalent bonds with thiols present in mucins under physiological conditions. The rationale behind these modifications was to enhance the mucoadhesive properties of chitosan and extend the retention time of drugs within the nasal cavity.

MATERIALS AND METHODS

Low molecular weight chitosan (Sigma-Aldrich, UK) was modified using MA and CA. The modification process involved adding different concentrations of these anhydrides to a 1% w/v chitosan solution prepared with 3% acetic acid. The mixtures were reacted overnight at 40°C and then purified by dialysis, followed by freeze-drying (Kolawole et al., 2018). The modified chitosan derivatives were characterized using ^{1}H NMR and FTIR spectroscopies. Turbidity and zeta potential measurements were performed with 0.15% w/v polymeric solutions to evaluate the solubility and charge properties at different pH levels. The mucoadhesive properties of the modified derivatives were assessed using a tensile test and fluorescein flow-through studies conducted on sheep nasal mucosa.

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RESULTS AND DISCUSSION

Chitosan and its derivatives were characterized using 1H NMR spectroscopy (Figure 1). The spectrum revealed signals for residual acetyl groups (1.9 ppm), protons in the glucosamine ring (2.8-4 ppm), methylene groups from the modified chitosan (1.7-1.9 ppm), and unsaturated groups (5.6-6.5 ppm) (Yu et al., 2007). The degree of chitosan substitution was determined based on the ^{1}H NMR analysis of the products.

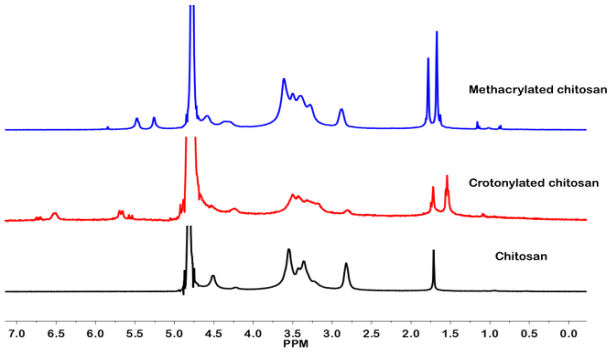

Figure 1: ^{1}H NMR spectra of chitosan, crotonylated and methacrylated chitosan recorded in D_20 acidified with trifluoroacetic acid.

Turbidity measurements were performed to investigate the solubility behaviour of chitosan and its derivatives at different pH levels. Interestingly, the chitosan derivatives exhibited distinct pH-solubility profiles compared to unmodified chitosan. The methacrylated derivatives showed a tendency to precipitate at higher pH values, while the crotonylated derivatives remained in colloidal suspension over a wide range of pHs. This observation, as reported by Sogias et al. (2010), highlights the influence of chemical modifications on the solubility characteristics of chitosan derivatives.

The modifications of chitosan resulted in reduced zeta potential values, with crotonylation showing a greater decrease compared to methacrylation. Spray drying of polymeric solutions with sodium fluorescein generated microparticles for texture analysis and flow-through studies (Figure 2,3). Both investigations demonstrated stronger mucoadhesive properties and prolonged retention of modified chitosan derivatives on the nasal mucosa compared to unmodified chitosan. Further studies will be performed to evaluate the toxicological properties of these new derivatives.

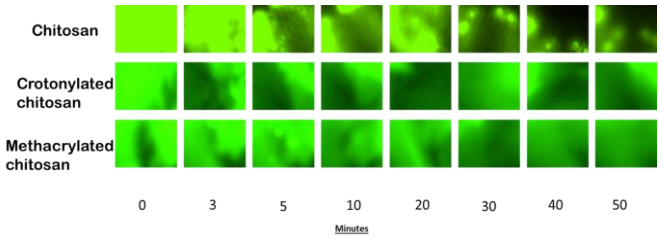

Figure 2: Fluorescent images of chitosan, crotonylated chitosan and methacrylated chitosan formulations with sodium fluoresceine at different time intervals during nasal retention studies.

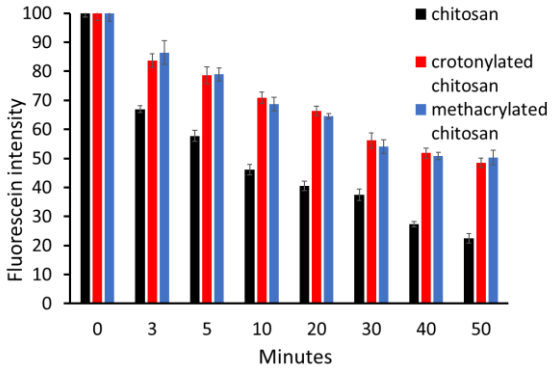

Figure 3: Fluorescence intensity data at different time intervals as analysed by Image J software.

CONCLUSIONS

The modifications of chitosan by reactions with methacrylic and crotonic anhydrides have resulted in changes in solution charge, pH-solubility profiles, and improved mucoadhesive properties. The modified chitosan derivatives demonstrated enhanced drug retention on the nasal mucosa compared to unmodified chitosan.

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