Catechol-Chitosan/Genipin Hydrogel as Mucoadhesive Buccal Drug Delivery System

J. Xu¹, S. Strandman², J. Barralet³ and M. Cerruti¹,³

¹Department of Mining and Materials Engineering, McGill University, Montreal, Quebec, H3A 0C5, Canada; ²Department of Chemistry, Université de Montréal, Montreal, Quebec, H3C 3J7, Canada; ³Faculty of Dentistry, McGill University, Montreal, Quebec, H3A 0Y7, Canada
jinke.xu@mail.mcgill.ca

ABSTRACT

A novel hydrogel made in catechol-modified chitosan (Cat-CS) crosslinked by genipin (GP) was developed as a mucoadhesive drug delivery system through buccal mucosa. Various techniques were used to characterize the hydrogel. Mucoadhesion and drug release properties were evaluated in vitro. The results have shown that Cat-CS/GP has enhanced mucoadhesion property, and is a promising system for buccal drug delivery.

EXPERIMENTAL METHODS

Cat-CS was synthesized from low molecular weight CS (M.W. 50,000 – 190,000 Da, Sigma) and hydrocaffeic acid by EDC coupling. Nuclear Magnetic Resonance (NMR) spectrum analysis had confirmed that 6% of the repeating units contained catechol groups. To prepare the hydrogel, Cat-CS was dissolved in deionized water at concentration of 1.5% (w/v). Genipin was mixed into the solution at weight ratio GP:Cat-CS of 1:20. The mixture was allowed to cure at 37 °C for 12 h. CS hydrogel was prepared as control.

The hydrogels were characterized by Fourier Transform Infrared Spectroscopy (FTIR), Solid-state NMR, and Scanning Electron Microscope (SEM). In addition, rheological experiments were conducted on AR2000 Rheometer with cone/plate steel geometry (Φ 40 mm, 2°). Storage and loss moduli (G’,G’’) were monitored via oscillatory time sweep of 12 h at 37 °C under constant stress and frequency.

Acetaminophen (AP, Alfa Aesar) was selected as a model water soluble drug to evaluate the release profile. AP was incorporated in the hydrogel during gelation. Cumulative release of AP was studied in vitro in PBS buffer with pH 6.8 at 37 °C. Each test was repeated 3 times.

In vitro mucoadhesion was evaluated based on adhesion time of hydrogel patches on pig buccal mucosal membrane. The hydrogels were cut in disks with diameter of 6 mm and...
thickness of 1 mm, and carefully pressed onto pig buccal mucosal membranes. The membranes were immersed in PBS buffer at pH 6.8 and stirred at 300 rpm. The time that was required to detach the hydrogel from the mucosa was recorded. Each experiment was repeated 6 times.

RESULTS AND DISCUSSION

FTIR and solid-state NMR confirmed the presence of catechol groups in Cat-CS. The catechol groups did not interfere during the crosslinking reaction of GP and –NH₂ of CS. SEM images showed that the freeze dried CS/GP and Cat/GP hydrogels had porous layered structures (Fig.1).

CS/GP and Cat-CS/GP hydrogels exhibited very different viscoelastic properties (Fig. 2). The gelation time (determined as the crossover point of G’ and G” in time sweep) of CS/GP hydrogel was ~100 min. The G’ of Cat-CS/GP was initially higher than G” and thus, Cat-CS solution was much more viscous and exhibited elastic character in contrast to CS. After 12 h of gelation, both gels reached the equilibrium, and G’ and G” of Cat-CS/GP were slightly higher than those of CS/GP, respectively.

The release profile of AP is shown in Fig. 3. Both CS/GP and Cat-CS/GP hydrogels had achieved sustained release of AP up to 2 h.

Figure 3. Cumulative release of AP from hydrogels in PBS pH 6.8 at 37 °C.

The addition of catechols significantly increased the adhesion of the hydrogels on the mucosal membrane: Cat-CS/GP hydrogels remained attached on the approximately 5 times longer than CS/GP.

CONCLUSION

Cat-CS/GP hydrogels are promising candidates as buccal drug delivery systems, showing enhanced mucoadhesion on pig mucosal membrane in vitro. In vivo evaluation is undergoing.

REFERENCES