J. Pharm. Pharmacol. 1998, 50 (Supplement): 171

Chitosan based hydrogels for macromolecular drug delivery

L. MARTIN, C. G. WILSON, F. KOOSHA* AND I. F. UCHEGBU

*Department of Pharmaceutical Sciences, University of Strathclyde, Glasgow G1 1XW, and *SmithKline Beecham Pharmaceuticals, Harlow, Essex*

Drug delivery via the buccal route is useful for gut labile drugs or drugs that undergo extensive first pass metabolism. The buccal mucosa is also less prone to damage or irritation than the nasal mucosa for example. Hydrogels are "hydrophilic natural or synthetic cross-linked polymers that have the ability to swell in an aqueous environment without dissolution", Knuth et al (1993), and they act as drug delivery systems by physically entrapping biomolecules, which are then slowly released. In this work a palmitoyl glycol chitosan, Uchegbu et al (1998), hydrogel is being developed for the delivery of gut labile macromolecules via the buccal route

Glycol chitosan was reacted with Palmitic acid N-hydroxysuccinimide (PNS) in a 1:2 and a 1:1 PNS, sugar monomer molar ratio to produce the amphiphilic polymers GCP12 and GCP11 respectively. The polymers were purified by ether extraction and exhaustive dialysis and an aqueous dispersion of both GCP11 and GCP12 freeze-dried in 96 well plates to produce gels. The gels are formed on freeze drying presumably due to the hydrophobic interaction of the palmitoyl units. GCP12 and GCP11 gel formulations were also made with varying concentrations of TPGS (d-alpha tocopherol polyethylene glycol succinate) and the substituted polyglycolized glyceride - Gelucire 50/13. These compounds were added to enhance drug penetration through the squamous epithelium.

GCP12 and GCP11 gels were hydrated and the percentage weight increase recorded. GCP12 gels have also been loaded with a model macromolecule FITC-Dextran (Mw ~ 4,000) by simply freeze drying a dispersion of the GCP12 in the presence of FITC-dextran. Dataon the release of this macromolecule will be presented.

GCP11 and GCP12 gels on hydration gave rise to a slowly eroding and swelling mass. GCP12 gels (prepared from a higher ratio of PNS) had a higher swelling capacity than GCP11 gels. The inclusion of Gelucire and TPGS within these chitosan-based gels decreased the swelling capacity and/or enhanced gel erosion, as exemplified by Figure 1. For GCP12/TPGS gels, only gels prepared with 60 or 65% GCP12 showed any appreciable swelling (Figure 1).

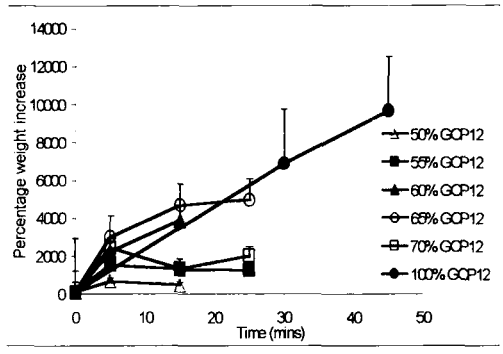

Figure 1:Swelling of various GCP12/TPGS gels in water.

These experiments demonstrate that slowly eroding but swelling hydrogels may be formed from amphiphilic chitosan molecules and the swelling capacity controlled by the initial level of hydrophobic modification and the presence of additives in the gels. Macromolecules may also be loaded onto these drug delivery gels by simple freeze drying techniques. Preliminary investigations indicate that the gels are bioadhesive in nature.

Knuth, K., Amiji, M., Robinson, J.R. (1993), Adv. Drug Del. Rev 11: 137-167

Uchegbu I.F., Schätzlein A.G., Tetley L., Gray A.I., Sludden J., Siddique S., Mosha E. (1998). J Pharm Pharmacol 50: 453-458.