THE IN-VITRO CHARACTERISATION OF MUCOADHESIVE HYDROGEL MATERIALS FOR THE BUCCAL DELIVERY OF PEPTIDES

S.J.Warren. I.W.Kellaway. *P.Timmins. Welsh School of Pharmacy, U.W.C.Cardiff. *Bristol Meyers Squibb, Merseyside. UK.

At present chronic therapy employing peptide drugs necessitates multiple daily iv dosing due to poor oral bioavailability. Alternative absorptive mucosa are currently being investigated as possible sites for peptide delivery eg nasal, rectal. The purpose of this study was to develop a delivery system tailored to the buccal mucosa. The advantages of this route include avoidance of hepatic first pass metabolism and proteolytic enzymes of the GI tract, easy accessibility and greater patient compliance (Veillard. et al 1987).

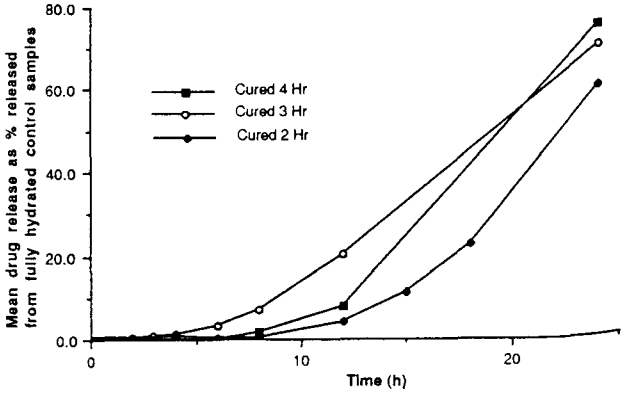
Mucoadhesive hydrogel patches have been formulated from a range of Poly(acrylic acid) (PAA:linear, mw 450000)/ sucrose blends (0.05-015g sucrose/g PAA), cast from solution and crosslinked via esterification to form glassy films. Gels with suitable mechanical properties in the swollen state could be easily handled. Those with desirable in vitro mucoadhesive performance, measured by the method of Hunt et al (1989) were selected for drug release analysis (Table 1). The nonapeptide oxytocin (mw 1007) was selected as the model drug as previous buccal formulations (Pitocin:Parke Davis) suggested its suitability.

Hydrogel samples were swollen to equilibrium in solutions of known oxytocin concentration (50-100μg/mL). Loaded gels were removed and rapidly dried in a vacuum desiccator (12h). Due to the adhesive nature of the materials and preferential drying of solvent from the non supported surface, gels dried in this manner were distorted. This was overcome by brief exposure (30s) of vacuum dried materials to a strong acid solution (2M HCl) followed by washing in acetone to remove traces of acid and drying to constant weight in a desiccator. The resultant drug loaded hydrogels possessed similar hydration properties to parent unloaded materials. Drug release profiles from hydrating gels were obtained under various conditions. Initially gels were swollen in a stirred 25mL reservoir of pH 7.4 citrate/phosphate buffer solution (22°C) and sampled periodically. Oxytocin was quantified using a fluorometric derivatization technique coupled with reversed phase HPLC. Rapid gel hydration resulted in equally rapid release of the drug (Table 1). To emulate in vivo conditions a Franz diffusion cell was employed with dialysis membrane supporting the hydrogel upon the receptor chamber containing 5.5mL pH 7.4 citrate/phosphate buffer solution (22°C). In this environment drug release was found to be sustained over a 24h period (Fig 1). Comparison of swelling profiles with drug release data suggest that the rate of solvent penetration rather than the crosslink density of the materials controlled oxytocin release.

Table 1. Swelling, mucoadhesive and drug release properties of hydrogels (0.15g sucrose/g PAA)

Gel cure time at 90°C (h)	Equilibrium swelling ratio	Mean Peak Mucoadhesive Force (N/cm ^{2}x10 ^{2})	Equilibrium Swelling Time (min)	Time for Total Release (min)
2	4.3	2.64	309	131
3	3.8	3.76	182	115
4	3.3	4.16	123	107

Fig 1. Drug release profiles for three hydrogel materials (0.15g sucrose/gPAA) in Franz diffusion cell pH7.4



Hunt, G. et al (1987) in Drug Delivery Systems:Fundamentals and Techniques. Eds Johnson, P. Lloyd-Jones, J. G. 180-199

Veillard, M. M. et al (1987) J. Cont. Rel. 6: 123-131