IN-VITRO INVESTIGATION OF THE POTENTIAL OF MUCOADHESIVE MICRO SPHERES FOR THE CONTROLLED NASAL DELIVERY OF OXYTOCIN

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The nasal mucosa has been used as an absorption site for drugs treating local infections for many years. Recently, its potential for peptide absorption has been realised, thereby avoiding first pass metabolism and proteolytic degradation experienced in the GI tract. The nasal mucosa offers a desirable site for the absorption of systemically effective drugs due to its numerous microvilli and rich vasculature. Cilia drive foreign particles and mucus rearward to the nasopharynx to be swallowed. In man, a nasally administered powder or solution has a half-life clearance of 20 min, which may be extended to ≥3 h for mucoadhesive microspheres (Illum et al 1988).

This work concerns the production and characterisation of mucoadhesive hydrogel microspheres produced by cross-linking polyacrylic acid (Carbopol 907) with maltose in a W/O emulsification process. Particles of varying cross-linker concentration and curing time were synthesised, and the use of palmitic acid and stirring at 1600 rpm gave microspheres 70% of which were in the range of 30.3-112.8μm (fig. 1), and would therefore be suitable for nasal deposition. Drug loading was achieved by placing the microspheres in a volume of oxytocin solution equivalent to that required for complete hydrogel hydration so that all of the drug present in solution was associated with the particles, which were subsequently dried to form a free flowing powder.

A Franz diffusion cell was used as an in vitro release model for nasal delivery since this would allow the mirospheres to hydrate slowly in an enclosed humid environment (25°C), with the particles lying on a dialysis membrane hydrated over a well of citrate-phosphate buffer solution (pH7.4), simulating the hydration of microspheres deposited on the nasal mucosa. Samples were derivatised with fluorescamine and analysed by HPLC. Drug release was sustained for at least 5 h. The rate of release of oxytocin from three samples (S.E.M.±4.5%) from a single batch of microspheres provided good reproducibility between samples. When the drug release profiles obtained for particles of varying [Malt]:[PAA] were compared, no trend in release rate could be detected. However, when the drug released from microspheres of similar [Malt]:[PAA] but different curing times were compared, it was evident that increased curing time gave rise to an increased rate of release of oxytocin as shown in fig. 2. It is possible that with increased curing time, the polymeric network inside the microsphere becomes heavily cross-linked and that swelling on hydration becomes severely limited. The oxytocin will therefore be surface associated instead of being uniformly distributed throughout the particle. This would also account for the low percentage of oxytocin released from the least cured particles, since these microspheres were not sufficiently hydrated under the experimental conditions to release all of the drug. Drug distribution within the microsphere is currently being examined.

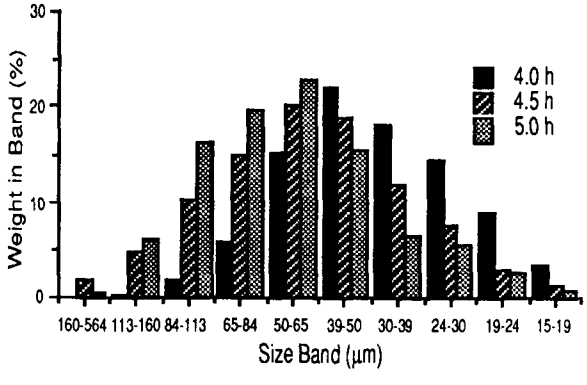

Fig.1. Size distribution of microspheres of [Malt]:[PAA] 1:10 with varying curing times.

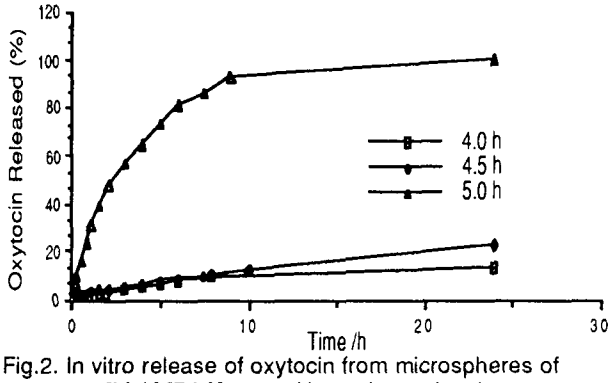

Fig.2. In vitro release of oxytocin from microspheres of [Malt]:[PAA] 1:10 with varying curing times.

Illum,L. et al (1988) Int. J.Pharm. 46, 261-265