Electro-responsive drug release from chitosan hydrogels and microparticles *in vivo*.

Sudaxshina Murdan* and Ismat Jahan
Department of Pharmaceutics, The School of Pharmacy, University of London, 29-39 Brunswick Square, London, WC1N 1AX, UK. Email: sudax.murdan@ulsop.ac.uk

'Smart' drug delivery vehicles which release their drug load in a predictable and reproducible manner, in response to an internal or external chemical, physical or biological stimulus, may provide optimised drug delivery, for example when mimicking the *in vivo* pulsatile release of endogenous chemicals, such as insulin. Electro-responsive drug release from hydrogels is being investigated in many laboratories, including our own and many *in vitro* studies have been published (for a review, see Murdan, 2003). Meanwhile, there has been only one *in vivo* study, showing drops in plasma glucose levels following two pulses of electrical stimulation of a subcutaneously implanted hydrogel containing insulin (Kagatani, 1997).

Our aim was to investigate the *in vivo* electrical responsiveness of chitosan hydrogel and microspheres. The latter have the advantage over hydrogels in that they do not need surgical implantation, but can be easily injected. Diclofenac sodium (DFNa) was used as the model drug.

Drug-loaded chitosan hydrogels and microspheres were prepared by methods modified from Ramanathan *et al.*, (2001) and from He *et al.*, (1999) respectively; the preparations are described in more detail in the abstracts Jahan et al. *In vitro* studies showed that the two formulations released loaded drug in response to an applied electric current (Jahan & Murdan, 2004). The *in vivo* studies were conducted on anaesthetised male Wister rats. The gel and the microspheres were hydrated in deionised water for 30 min and 24 h respectively prior to surgical implantation (gel) or subcutaneous injection (microspheres) under the shaved abdominal skin. Pulses of electrical current (0.4mA, 0.5mA/cm^2) were then applied for 10 min at 0, 30, 60 and 90 min using Ag/AgCl resting ECG electrodes placed on the shaved skin of the animal. The anode was placed on top of the implant while the cathode was placed 2 cm away, still on the shaved abdomen. The experiment was followed for 2h. Blood samples were taken from the tail vein at time zero and after every electrical stimulus and the plasma was analysed for diclofenac sodium by HPLC. Passive release experiments (control) were conducted in the same way, except that no electric current was applied.

We found that
i) under passive conditions, some drug was released from both hydrogel and microspheres, probably due to diffusion along the concentration gradient,
ii) upon electrical stimulation, drug release from both hydrogel and microspheres was increased with respect to passive conditions. This is attributed to drug electrophoresis towards the oppositely charged electrode (gel and microspheres) and electro-induced gel deswelling, with concomitant expulsion of drug from the hydrogel.
ii) a pulsatile electro-responsive release of the drug was obtained from the hydrogel, but not from the microspheres formulation,
iii) with repeated electric pulses, the extent of drug release from the hydrogel decreased. This could be due to reduced gel responsiveness and deswelling and/or reduced drug content in the hydrogels.
iv) electrical stimulation of microspheres resulted in a burst drug release, followed by a slow and steady release. This profile mirrored that of the control experiment, except that it was twice the extent of passive release.

To conclude, we have shown a pulsatile electro-stimulated drug release profile from chitosan hydrogel. A pulsatile release was not shown from microspheres; however, drug release was higher under the influence of an electric current. Further work should be conducted to optimise the electro-responsive drug release *in vivo*.

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