In vivo Electro-stimulated Release of a Model drug from Chitosan Hydrogel

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Interest in responsive hydrogels for utilisation as smart drug delivery system has increased to meet the need for better control of drug delivery. Hydrogels composed of polyelectrolytes respond to the application of an electric current and release drug via changes in gel composition such as gel collapse, syneresis and rheological behaviour. The electro-responsive release of drugs in vitro from chitosan hydrogels have been previously reported by Ramanathan et al (2001) and ourselves (Jahan *et al*, in press).

In this abstract, we report on the *in vivo* electro-responsive release of a model drug, diclofenac sodium (DFNa) in rats, from chitosan hydrogels.

Drug-loaded chitosan hydrogels were prepared at room temperature (~25°C), following a method modified from Ramanathan *et al*(2001), by reacting chitosan, ethanol, and acetic anhydride. High molecular weight chitosan (hMr; Mr ~ 600,000) at 0.5% w/v, was dissolved in 4 ml of 10% v/v acetic acid solution. The viscous chitosan solution was diluted with 6 ml of ethanol and gelation was induced with 0.70-mmol (66 µl) of acetic anhydride. The mixture was then transferred into a Teflon mould and left undisturbed overnight. The gels were homogeneous, transparent, colourless and firm to the touch. DFNa was loaded in the gel as part of the reaction mixture at a concentration of 0.2% (w/v). The drug was dissolved in the ethanol component of the reaction mixture prior to the addition of acetic anhydride.

The DFNa-loaded chitosan hydrogel was hydrated by placing the gel in deionised water for 30 min and then (~2×2×10 mm) was surgically implanted subcutaneously under the shaved abdominal skin of anaesthetised male Wister rats (210-230g). The surgical incision was sealed using cyanoacrylate adhesive. Pulses of electrical current (0.4 mA, 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 DFNa by High Performance Liquid Chromatography. Passive release experiments (control) were conducted in the same way, except that no electric current was applied.

We found that DFNa could be released from chitosan hydrogel in a pulsatile fashion in response to repeated pulses of electrical stimuli. Some release of DFNa during the "off" period was also observed, probably due to drug diffusion along a concentration gradient. The electro-stimulated release of DFNa is attributed to syneresis of the gel, with concomitant drug expulsion and/or due to electrophoresis of the negatively charged drug towards the anode. This reflected passive drug release, again along a concentration gradient, in the control experiments. At the end of the experiment ~70% of DFNa was released from the implant which was electro-stimulated while ~40% was released under passive conditions.

In conclusion, we demonstrated the pulsatile drug release from an electro-responsive chitosan hydrogel *in vivo*, in rats. Such stimulated release in vivo, has only been reported once before (Kagatani,S *et al*,1997)

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