Electro-responsive drug release from chitosan hydrogels and microparticles in vivo.
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‘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/cm²) 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.
iii) a pulsatile electro-responsive release of the drug was obtained from the hydrogel, but not from the
microspheres formulation,
iv) 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.

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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