Electro-stimulated Release of Anionic and Cationic Drugs from Chitosan Microspheres

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Abstract Summary

Chitosan microspheres, entrapping diclofenac sodium or metformin hydrochloride were produced by spray drying. The release of the drugs under the influence of constant current was investigated. The release of diclofenac sodium from the microspheres could be increased under the influence of electric field while the release of metformin hydrochloride could not be electro-controlled.

Introduction

Hydrogels have been extensively investigated as electro-stimulated drug delivery systems (DDS). These gels have to be implanted. To make this DDS more patient-friendly, hydrogels can be fabricated into microparticles, which can be injected rather than surgically implanted.

In this work, attempts have been made to formulate chitosan (CS) microspheres entrapping an anionic drug, diclofenac sodium (DFNa) or a cationic drug, metformin Hydrochloride (Met HCl), and to establish if the release of these drugs from the particles can be electro-controlled

Methods

Preparation of Chitosan Microparticles

Microspheres of low molecular weight CS (Mr ~150,000) were prepared by a method modified from He *et al*., (1999). CS was cross-linked with glutaraldehyde and was subsequently spray dried. Drug-loaded CS microspheres were prepared by the addition of Met HCl or DFNa to the CS solution prior to the addition of the cross-linker. The influence of glutaraldehyde concentration on microsphere properties (e.g. surface morphology size, zeta potential, drug loading and release) was determined.

Characterisation of Microspheres

Microspheres were sized using Malvern Mastersizer and morphology was analysed using Scanning Electron Microscopy. The zeta potential of the microspheres was measured by Malvern ZetaMaster. To enable the conduction of electricity within particles, the latter were hydrated in deionised water and the change in their size was monitored using Malvern Mastersizer.

Release of Diclofenac Sodium or Metformin HCl from Microspheres

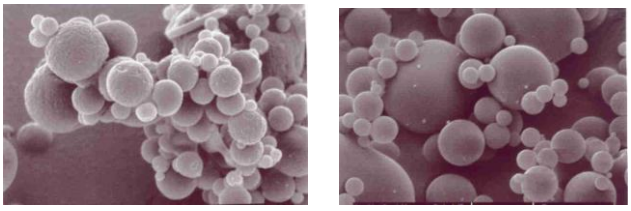
Release experiments were conducted at room temperature in deionised water using a custom-made Franz Diffusion Cell. 5 mg of the particles were hydrated in 3 ml of deionised water and then placed in the donor chamber of the diffusion cell. Pulses of electric current (0.4 mA, 30 min on, 30 min off) were applied to the donor chamber using two carbon electrodes and the drug release was followed for 6 h by taking samples of the receptor medium every 30 min. The samples were replaced by adding an equal volume of water to the receptor chamber. The passive release experiments were conducted in the same way except that no current was applied. The release experiments of DFNa and Met HCl from different formulations was determined in triplicate and the mean obtained

Results and Discussion

Increasing concentration of gluteraldehyde:

- had no significant effect on particle size and charge. The particles were 3-5 μm in diameter and had zeta potential of 35-42 mV.

- had effect on surface morphology of the particles. Particles had good sphericity but less cross-linked particles had wrinkles on their surface while higher cross-linked had smooth surface morphology . For example, morphology DFNa and Met HCl loaded microspheres cross-linked with 2% and 16% glutaraldehyde are shown in figure 1.



(a) (b)

Figure 1. Scanning electron micrograph of DFNa loaded chitosan microspheres cross-linked with (a) 2% gluteraldehyde and (b) 16% gluteraldehyde cross- linked.

- The entrapment efficiency of the particles for Met HCl and DFNa decreased with increasing concentration of cross-linker in the formulations. For example, 2% cross-

linked particles had entrapment efficiency of 60-70% while 16% cross-linked particles had entrapment efficiency of 20%.

• Swelling of the particles decreased with increasing concentration of glutaraldehyde. Maximum swelling was achieved in 24 h and 96 h for low and high cross-linked particles respectively.

• Higher cross-liked particles were less sensitive to electric current than lower cross-linked particles The electro-stimulated release of DFNa was found to be higher than the passive release for all formulations. Figure 2 shows a few examples. When electric field is applied, the negatively charged DFNa electrophoresed towards the anode and diffuse out of the particles. Once the current was switched off, the drug continued to diffuse out of the gel, probably due to the concentration gradient of drug between the particle and the external medium. At the end of the experiment, less than 10-20 % of the drug was released.

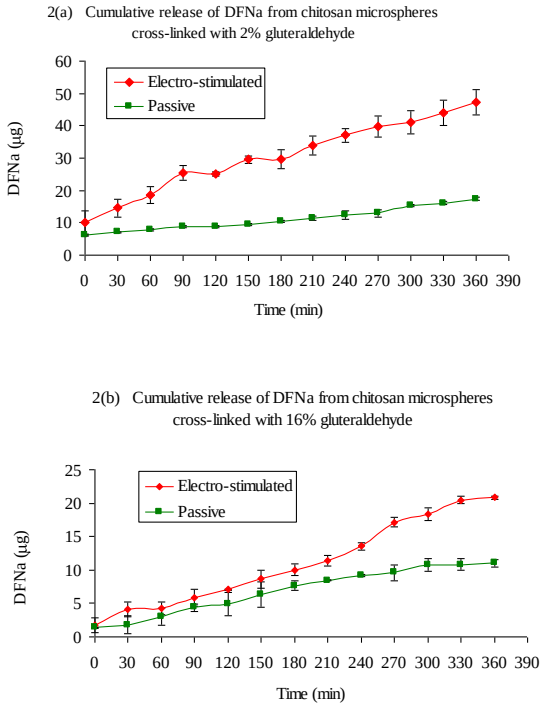


Figure 2. Electro-stimulated and passive release of DFNa from chitosan microspheres

• In contrast to DFNa, the electro-stimulated and passive release profile of Met HCl from the microspheres were similar to each other (figure 3). This is because Met HCl, being cationic, is not ionically bonded to the polymer backbone and may even be repelled by the positively charge CS polymer. Thus the drug easily diffuses out of the gel network when the current is switched off. This phenomenon is established by the fact that 60-80% of the drug was released at the end of the experiment.

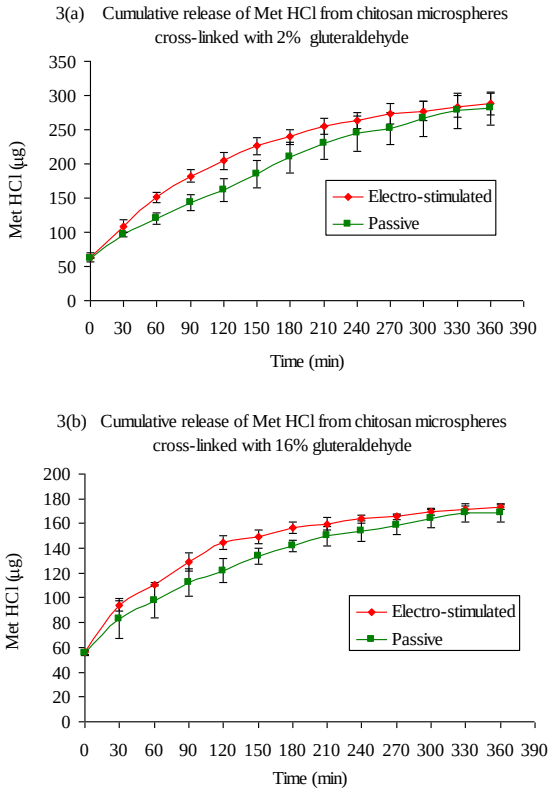


Figure 3. Electro-stimulated and passive release of Met HCl from chitosan microspheres.

Conclusions

The release of Met HCl from chitosan microspheres could not be electro-controlled while the release of DFNa could be increased when electro-stimulated.

Future work would involve establishing if the release of DFNa could be electro-stimulated *in vivo* and to investigate if an "on-off" pattern of drug release could be obtained *in vivo*.

Reference

He, P., Davis,S.S.,Illum,L.,(1999)Int.J.Pharm,187:53-65