Towards the development of pulsatile release systems for teriparatide

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Background: Teriparatide (and analogue peptides) are the only FDA approved anabolic treatments for osteoporosis. Current therapies are administered as a daily subcutaneous injection, whereby the frequent invasiveness of this administration route results in poor patient adherence and limits clinical efficacy. Controlled release systems have the potential to reduce the frequency of administration, but to achieve the desired anabolic effect such a system must ensure a pulsatile release profile with brief plasma spikes approximately once every 24 h.
Thermo-responsive formulations (e.g. liposomes) undergo a temperature-related phase-transition which is thought to allow active control of the release of therapeutics and has been the centre of extensive research in the field of oncology. These systems may also present a promising approach in the development of pulsatile release systems. Here, thermo-responsive liposomes were investigated for their potential to actively control the release of an entrapped peptide therapeutic.

Methods: Teriparatide was initially precipitated from aqueous solution with a surfactant before resuspending it in ethanol. The peptide was added to an ethanolic solution of phospholipids and liposomes were prepared by thin-film rehydration and extrusion. Free peptide was removed from the liposome formulation by dialysis. The transition temperature of the liposomes was tailored by alteration of the phospholipid composition. The prepared liposomes were characterized for peptide entrapment, size distribution, and transition temperature. Further, the release profile at different temperatures was determined and the functionality of the released peptide assessed in a newly developed assay overexpressing the peptide's receptor in a HEK293 cell model.

Results: The prepared liposomes were small (< 200 nm) and monodispersed (PDI < 0.2) and achieved a teriparatide entrapment efficiency of 77.4 ± 5.7%. Transition temperatures (Tc) in the range of 41-51 °C were obtained. The release of the entrapped peptide was shown to be temperature dependent and modifiable with phospholipid composition. A HEK293 model in which the peptide receptor (PTH1R) is overexpressed was successfully developed, and a stable cell line was created for functional performance assessment.

Conclusions: Thermo-responsive liposomes were prepared, and teriparatide was successfully entrapped within the liposomes. Peptide release was shown to be temperature dependent providing a first proof-of-concept of the suitability of thermo-responsive liposomes for pulsatile delivery.