Peptide Functionalised Chitosan Nanoparticles for co-delivery of siRNA and methotrexate for the treatment of Psoriasis

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Background: Psoriasis is a chronic, inflammatory, and immune regulated disease, with current treatments having both limited efficacy and association with unwanted side-effects. IL-17A is an inflammatory cytokine, key to psoriasis pathogenesis and disease maintenance. Research has shown that targeting IL-17A and its receptor can be an effective treatment for psoriasis. Short-interfering RNA (siRNA) based therapeutics have garnered interest as a means to target IL-17A/receptor via RNA interference. Methotrexate (MTX) is a long-standing treatment option for sufferers of moderate/severe psoriasis and is shown to improve psoriasis area and severity index (PASI) scores, however its use is currently limited by systemic side-effects. The skin represents an attractive route for the delivery of psoriasis treatment, due to its non-invasive nature, ease of access, it being the site of intended action and avoidance of the gastrointestinal tract. It is hypothesised that the co-delivery of siRNA and methotrexate will have a synergistic effect, leading to improved therapeutic outcome. Chitosan (CT) nanoparticles (NPs) possess properties that could enable them to facilitate topically applied, dermal delivery of drugs. This is beneficial as it allows treatment to be targeted to the site of disease, as well as reducing systemic side-effects. Peptides have been used to functionalise NPs, improving their capacity for cell penetration or targeting specific tissue. One such example is the AT1002 tight junction opening peptide. This project aims to develop a new treatment strategy for psoriasis, based on development of peptide functionalised chitosan nanoparticles for co-delivery of siRNA and methotrexate to the skin. In addition, to evaluate the effectiveness of the method through in-vitro and ex-vivo studies.

Methods: MTX-loaded CT NPs were formulated using the ionic gelation method. The effect of cross-linker type, concentrations of the polymer and cross-linker on the particle size and zeta potential, and the percentage entrapment efficiency were investigated. The selected MTX/CT NPs were functionalised with AT1002, which was synthesised using a CEM Liberty Blue microwave-assisted solid phase peptide synthesiser, and subsequently characterised by HPLC and MS.

Results: Our results showed that controlling formulation parameters has enabled particles 200-500 nm to be produced, with low PDI values and a positive zeta potential, showing entrapment efficiency ~ 90% with desirable properties for skin delivery. These NPs were characterised using X-ray diffraction, dual-scanning colorimetry and moisture absorption/retention behaviour assessed.

Conclusions: In conclusion, peptide functionalised MTX/CT NPs show suitability for future research into skin delivery of siRNA and MTX for the treatment of psoriasis.