PEGYLATED AND THIOLATED CHITOSAN NANOPARTICLES FOR ORAL
DELIVERY OF PTH 1-34

ABSTRACT
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May 2014

Nanoparticles composed of naturally occurring biodegradable polymers have emerged as potential carriers of various therapeutic agents including peptides and proteins for controlled drug delivery through the oral route. Chitosan (CS), a cationic polysaccharide, is one of such biodegradable polymers, which has been extensively exploited for the preparation of nanoparticles for oral controlled delivery. However, the high solubility of CS at low pH of stomach impedes the delivery of therapeutic proteins and peptides to the intestine. To overcome this problem, CS derivatives have been developed in the long run, which not only protect the proteins from degradation in the gastrointestinal tract but also provide a sustained release delivery platform. NPs should remain intact during their transit through the stomach for the effective delivery of proteins and peptides and should be able to protect their degradation by proteolytic enzymes. Although CS is one of the most commonly exploited polymer for the oral delivery of insulin, the focus has recently shifted from CS to CS derivatized biomaterial for the oral delivery of proteins and peptides. The use of CS derivatives for oral nanoparticle preparation vastly improves properties, such as better drug retention capability, improved permeation, enhanced mucoadhesion and sustained release of therapeutic agents. CS derivatized polymers synthesized and used in our this thesis work are Thiolated chitosan (TCS) and PEGylated Chitosan (PEG-CS).
PTH 1-34 is a 4117 dalton small peptide which is a fragment of the parathyroid hormone PTH 1-84. It is used for the treatment of osteoporosis, osteoarthritis and is in trials for the treatment of hypoparathyroidism. The current subcutaneous injections of PTH 1-34 holds poor patient compliance and has urged the need for more compliant oral delivery vehicles for the peptide without compromising its biological functions. Researchers are advancing in formulating oral therapeutics of PTH 1-34. The use of absorption enhancers such as 8-(N-2-hydroxy-5-chlorobenzoyl)-amino-caprylic acid (5-CNAC) and PLGA microparticles for oral administration has been documented whereas the use of polymeric nanoformulation have not been reported.

Therefore this PhD thesis mainly focuses on the challenges in entrapping small peptide PTH 1-34 into the CS, TCS and PEGylated CS polymeric nanoparticles (NPs). In vitro and in vivo comparison between the modified and unmodified CS nanoparticle system has been depicted as proof of concept. A detailed account of the synthesis and characterization of the nanoformulation, in vitro toxicity profile and a record of the bioactivity of the released peptide has been experimentally proven in Human Primary osteoblast and osteosarcoma cell lines. All the formulations were orally administered independently in female Sprague dawley rats and the bioavailability and pharmacokinetic profile of the peptide was determined using the human specific PTH 1-34 ELISA kit and PK deduction software. The GI transit of the nanoformulations were parallely tracked.

The PEG-CS PTH NPs and TCS-PTH NPs were finally confirmed to be efficient oral delivery vehicles for PTH 1-34.