CHAPTER 4

SUMMARY

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FUTURE PERSPECTIVES
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SUMMARY AND FUTURE PERSPECTIVES

4.1 Summary

The research work done for this thesis focused on the development of PEGylated and Thiolated CS nanoformulations for the oral delivery of PTH 1-34 which is an FDA approved anabolic therapeutic peptide for the treatment of osteoporosis. We started with trials to entrap PTH 1-34 into CS which was successfully synthesized by simple ionic gelation method using TPP as a cross linker. In the next stage PEG-CS-PTH NPs and TCS-PTH NPs was formulated and these nanosized spherical particles were found to be biocompatible and haemocompatible under in vitro conditions. From the in vitro release data it was evident that the pH, volume of the release medium, diffusion and swelling of the NP systems influenced the concentration of the peptide released. The released PTH 1-34 was tested and confirmed to retain significant bioactivity as shown by elevated cAMP levels in NPs treated HOB cells. This second messenger activation in turn increased the cellular levels of bone specific alkaline phosphatase, osteocalcin, and calcium.

The attempt to orally deliver anabolic dose of 20 micrograms PTH 1-34 in rats was successfully accomplished using the PEG-CS PTH NPs and TCS-PTH NPs as proved by the pharmacokinetics data obtained from the rat blood samples and NIR images of its gastrointestinal transit. Precisely PEG-CS-PTH NPs and TCS-PTH NPs has overcome the barriers of the GI tract and delivered the peptide up to 12 h which is a time span that is several fold the normal elimination time observed in the subcutaneously administered
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PTH 1-34 (3h clearance). These findings affirmatively imply the potential of these CS based systems to release biologically functional levels of peptide in the *in vivo* rat models by benefiting from its mucoadhesive and paracellular transportation properties.

The discrepancy is that PTH 1-34 in anabolic dose and an intermittent plasma concentration pattern is what approves the peptide as an anabolic agent for retarding the progression of osteoporosis. A deviation from any one of these criteria pushes the peptide to the edge of being a catabolic agent which can aggravate bone resorption. In this work we have observed that, though an anabolic dose of PTH 1-34 was delivered by the PEG-CS and TCS systems, a prolonged 12 h circulation of picogram levels in blood was observed.

To summarize, the PEG-CS and TCS NP systems were efficient carriers of PTH 1-34 which protected the peptide, maintained its bioactivity and efficiently delivered PTH 1-34 orally.

4.2 Future Perspectives

- Studies focusing on the variation in oral absorption, clearance and PK profile in larger mammalian osteoporotic models could be compared to the results obtained here.
- Clinical studies in humans to evaluate the efficiency and efficacy of the nanoformulation as an oral therapeutic drug for osteoporosis.
- Endocrine disorders like Primary and secondary hypoparathyroidism, also demands PTH 1-34 delivery.