

DESIGN OF SURFACE-MODIFIED LIPID NANOSTRUCTURES FOR ORAL CALCITONIN DELIVERY

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INTRODUCTION: The use of submicrometric carriers has been proposed as a promising approach for overcoming the biopharmaceutical limitations that prevent peptide therapeutics from being successfully administered by the oral route¹. This experimental work was aimed at studying the influence of surface characteristics of new lipid-based colloidal carriers on their efficacy as peptide delivery systems². Concretely, we have designed two new nanocarrier systems consisting of a solid lipid core (tripalmitin) and a hydrophilic coating, either (poly (ethylene glycol) (PEG) or chitosan (CS) for the oral delivery of salmon calcitonin (sCT).

METHODS: Lipid nanoparticles were prepared by a double-emulsion solvent evaporation technique as described elsewhere³. The PEG coating was achieved by the adsorption onto the lipid cores of the modified amphiphile PEG-stearate. On the other hand, CS-coated nanoparticles were formed by means of the ionic interaction between the polycationic CS and the polyanionic surface of the lipid particles. The granulometry of the resulting systems were characterized by photon correlation spectroscopy, and the nanostructure of the carriers, including the composition and disposition of the surface molecules was characterized by electron microscopy, laser doppler anemometry and liquid-state NMR. The behaviour of the prepared systems was investigated "in vitro" following incubation with simulated gastrointestinal fluids with enzymes. Moreover, the ability of these nanoparticle carriers enhance the permeability of hydrophilic molecules through the intestinal epithelium was tested in the Caco-2 cell line. Finally, these carriers were loaded with sCT and their capacity to encapsulate and release this peptide was studied. These loaded formulations were then administered to rats to check the capacity of these carriers to enhance the pharmacological response to the peptide "in vivo".

RESULTS: The physicochemical characterization data evidenced the effective surface modification of these nanocarriers either with PEG or CS. Both carriers showed a great capacity to associate the model peptide salmon calcitonin. The nanosystems

developed were acceptably stable in gastrointestinal fluids and able to interact with Caco-2 cell monolayers irrespective of the coating composition. However, only those coated with CS showed permeation enhancing properties when applied in high concentrations to the Caco-2 cell monolayer. Finally, the results from the "in vivo" experiment indicated that CS-coated systems were very efficient at increasing the systemic absorption of salmon calcitonin, as revealed by the significant decrease in the serum calcium levels, whereas those coated with PEG resulted ineffective (Fig. 2).

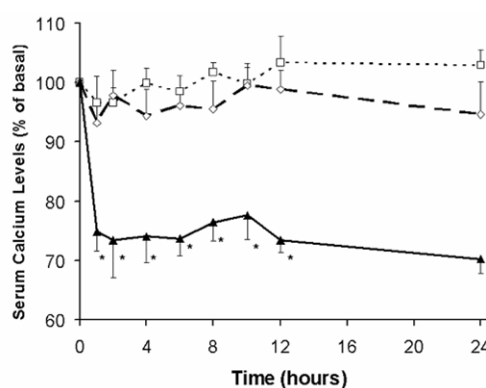


Fig. 2: Serum calcium levels (% of basal) in rats after administration of 500 UI/kg of (□) sCT in solution, (◇) sCT in PEG-coated nanoparticles and (▲) sCT in CS-coated nanoparticles (Mean \pm SD, n=6). *Significantly different ($\alpha < 0.01$).

DISCUSSION & CONCLUSIONS: Surface characteristics have shown to play a key role on the interactions of nanoparticles with the fluids and mucosal surfaces of the gastrointestinal tract. Altogether, these results suggest that CS surface-modified nanoparticles have a promising future for the oral delivery of peptide drugs.

REFERENCES: ¹ A. T. Florence and N. Hussain (2001) *Adv Drug Deliv Rev* **50** (Suppl.1):S69-S89. ² C. Prego, M. García, D. Torres and M. J. Alonso (2004) *J Control Release* **101**: 151-162. ³ M. Garcia-Fuentes, D. Torres, and M. J. Alonso (2002) *Colloid Surf B: Biointer.* **27**:159-168.

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