Improved Oral Absorption of Exenatide using a Novel Nanoencapsulation and Microencapsulation Approach

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Oral delivery of peptides remains challenging and continues to be one of the most attractive alternatives to their parenteral delivery. Despite intensive efforts invested over the last two decades, no commercial solution has yet emerged due to several drawbacks and hurdles associated with the poor intestinal membrane permeability of these hydrophilic macromolecules, instability in the gut and rapid metabolism. Therefore, the development of sophisticated delivery systems for oral administration of peptidic drugs still remains an attractive scientific challenge. Exenatide is a 39-amino-acid peptide approved as an adjunctive therapy for patients with type-2 diabetes failing to achieve glycemic control with oral antidiabetic agents. Exenatide is injected subcutaneously (SC) twice a day and can induce pain and possible infections at the sites of injection that could adversely affect patient compliance. A once-a-week injection of exenatide has been developed but still suffers from the aforementioned drawbacks. In the present research, we propose a nano/microencapsulation process of the hydrophilic bio-macromolecule to protect and control exenatide release. This unique strategy should facilitate the controlled release of the exenatide-loaded nanoparticles (NPs), as opposed to the release of the dissolved drug, in the vicinity of the mucosa in an attempt to avoid GI acidic and proteolytic enzymes degradation of the peptide. The first line of protection was achieved by loading the peptide into primary NPs. Different types of NPs were prepared; bovine serum albumin (BSA) NPs cross-linked with glutaraldehyde, BSA mixed with dextran NPs cross linked with sodium trimetaphosphate and conjugation of exenatide to poly-lactic-*co*-glycolic acid (PLGA) NPs. The second line of protection was achieved following encapsulation of the primary NPs within microcapsules consisting of a blend of Eudragit L 55-100 and hydroxypropyl methyl cellulose (HPMC) using a spray drying technique.

The primary NPs and microcapsules containing exenatide NPs were imaged by Cryo-TEM and SEM respectively. The mean diameter of the cross-linked NPs ranged between 50-100nm or 300-500 nm depending on the cross-linker and matrix. The PLGA NPs mean diameter was 90-150nm. The zeta potential value was around -45mV and the encapsulation yield was above 30-40% irrespective of the formulation. The *in vitro* release kinetic profiles showed that it was possible to reduce the burst release depending on the type of formulation up to 20% followed by a gradual slow release over 6-8 h. The pharmacokinetic results allowed to identify an optimal formulation based on dextran/BSA cross-linked NPs embedded in microparticles which elicited significant plasma levels following oral administration in rats. The marked increase in the oral bioavailability of such a formulation is promising, confirming that the peptide was not markedly degraded during the manufacturing process and the transit via the gastro-intestinal tract.