Design of a prototype delivery system to improve oral bioavailability of poorly permeable peptides

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Background:

Therapeutic peptides are a macromolecular drug category that exhibit good safety, efficacy and tolerability. However, low oral bioavailability and the requirement for parenteral formulations is a drawback to their widespread therapeutic application. Low oral bioavailability is caused by pre-systemic degradation and low passive permeation across the intestinal epithelium. This study aims to develop a dual delivery approach to increase intestinal permeation. The first step involves increasing lipophilicity via hydrophobic ion pairing (HIP) and solubilisation in a lipid based formulation (LBF). Partitioning of a peptide in a LBF can protect from enzymatic degradation whereas physical hydrophobisation may increase passive transcellular permeation. The second step involves inclusion of a permeation enhancer (PE) to accentuate passive transcellular permeation.

Methods:

The preparation of lipophilic salts was initially performed with the model peptide, vancomycin, using the amphiphilic counterions sodium docusate and sodium 1-dodecane sulfonate. The physicochemical properties of HIP complexes were tested using drug characterisation techniques, including precipitation efficiency, solubility screening, logP, and pH dependent dissociation. Peptide salts were then incorporated into a panel of self-emulsifying drug delivery systems (SEDDS), which were then evaluated by droplet size, zeta potential, PDI, self-emulsification ability and solubility of lead HIPs. Concurrently, a screen of novel PEs was performed in Caco-2 monolayers.

Results:

HIP increased LogP of vancomycin, 1.8-fold with vancomycin docusate and 2-fold with vancomycin dodecane sulfonate ($p < 0.0001$). The complexes did not completely dissociate in simulated GI fluids. There was increased solubility of vancomycin salts in vehicles used in the preparation of LBFs. Preliminary SEDDS demonstrated rapid spontaneous emulsification (<1 min) in simulated intestinal fluids and selected dispersions were within the nano size range, with uniformity values of less than 0.3 and negative zeta potential values. The PE screen identified novel trehalose esters with enhancement action of a macromolecule marker comparable to leading PEs in clinical development.

Conclusions:

HIP increased the lipophilicity of vancomycin and enabled increased loading in selected SEDDS. A panel of novel trehalose esters that are compatible with SEDDS were shown to improve macromolecule permeation in Caco-2 monolayers. Ongoing research involves further characterization of peptide salts, SEDDS optimisation and PE compatibility studies. Lead delivery systems will then be evaluated in Caco-2 monolayers and in isolated rat colonic mucosae.