

Oral peptide and protein delivery: unfulfilled promises?



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Oral delivery of peptides and proteins has long been dubbed the 'Holy Grail' of drug delivery, showing great potential but also presenting problems in development. Various factors, including permeability, stability and transit time in the gastrointestinal (GI) tract, can affect the absorption of orally delivered peptides and proteins but molecular size is generally considered to be the ultimate obstacle. However, there are polypeptide drugs, such as cyclosporin A and desmopressin that are available in oral dosage forms, indicating that polypeptide size should not be an absolute limitation. Hence, oral delivery of peptides and proteins remains an attractive option, but to reach its full potential, the challenges must be overcome.

Four general approaches – formulation, encapsulation, macromolecular conjugation and chemical modification – are currently being considered for improving peptide and protein absorption in the GI tract, and these are described in turn below.

Formulation

Penetration enhancers and protease inhibitors in peptide drug formulations have been investigated for many years. This approach focuses on changing the permeability or digestibility of a peptide to increase absorption in the GI tract. These agents can alter the integrity of the mucosal surface and can cause unacceptable side effects either systemically or locally.

Recently, new formulation components have been developed that do not act on the intestinal epithelium but

rather on the peptide molecules. For example, Emisphere Technologies (<http://www.emisphere.com>) has created a series of transport carriers, designed to form a complex with the polypeptide, thereby altering the structure of the polypeptide to a 'transportable' conformation [1]. According to a recent press release from Emisphere, a Phase IIa study of calcitonin, using their technology, [co-developed with Novartis (<http://www.novartis.com>)], demonstrated a significant reduction in markers of bone resorption in a dose-response fashion in 277 post-menopause women. This is an encouraging development. However, the mechanism of transport, the bioavailability of the drug, and the structure-activity relationship of the carrier molecule for various polypeptides, remains unclear.

Encapsulation

Peptide encapsulation technology in particulate carriers has been developed extensively over the past few years. As a result of their stability in the GI tract, solid microparticles or nanoparticles appear more favorable than liposomes for oral delivery, and two types of particle, chitosan [2] and hydrogels [3], have recently drawn much attention. These particles appear to be effective for oral vaccine delivery where the particles are likely to be absorbed at the area of Peyer's patches in the GI tract, and subsequently targeted to the immune system [2]. However, in general drug absorption, more work needs to be done regarding the efficiency and mechanism of either transcellular or paracellular transport in the GI epithelium and regarding the systemic release of drugs following absorption.

Macromolecular conjugation

Polypeptides can be conjugated to a macromolecular carrier, such as a polymer or a protein. The advantage of using conjugation technology for improving peptide GI absorption is that it will change only the molecular properties of the drug, not the function of epithelial cells, and might therefore avoid some of the side effects observed in using penetration enhancers. Amphiphilic polymers, such as alkylated polyethylene glycol derivatives, have been developed by NOBEX (<http://www.nobexcorp.com>); their insulin oral delivery system, co-developed with GlaxoSmithKline (<http://www.gsk.com>), is in mid-Phase II clinical trials and preliminary reports are promising.

To develop this technology further, into a therapeutically acceptable dosage form, more information regarding bioavailability and transport mechanism is needed. Considering their size and the amphiphilic properties, these polymers might possess very complicated mechanisms for GI absorption. Proteins such as transferrin [4] and lectins [5] have also been suggested as transport carriers in GI absorption of polypeptides. These protein carriers probably require transcytosis to be transported across the intestinal epithelial barrier and the efficiency of this process can be a limiting factor for developing such absorption carrier systems for drug delivery. Even though there are agents that can increase specific receptor-mediated transcytosis, toxicity problems similar to those seen with penetration enhancers might arise.

Chemical modification

Modification of proteins using small molecules is another recent development in oral absorption technology. For example, cobalamin-protein conjugates have been proposed as a GI delivery system via the normal vitamin B₁₂ absorption pathway, which involves the formation of a complex between the conjugate and a gastric-released intrinsic protein factor. The subsequent binding to intrinsic-factor receptors on GI epithelial cells can lead to the absorption of the cobalamin-protein conjugates [6]. The drawback of this delivery system is the low number of intrinsic-factor receptors in the GI tract, resulting in poor efficiency. However, this could be overcome by combining the intrinsic-factor-receptor-mediated transport with the use of polymers or nanoparticles to increase the loading of drug per cobalamin, an approach currently being investigated by Access Pharmaceuticals (<http://www.accesspharma.com>). Lipids, such as bile acids and fatty acids, are another type of small molecule that has been used to modify polypeptides for increasing oral delivery.

Lipidization of a polypeptide appears to be a reasonable approach for developing oral delivery system, because there are examples of natural peptides with high lipophilicity, such as cyclosporin A, that can be absorbed in the GI tract. In addition, lipidization can increase the stability of a peptide against digestion in the GI tract. One of the limitations of this method is that lipid modification can reduce the biological activity of a peptide. Thus, a reversible lipidization technique has recently been developed to ensure the regeneration of active polypeptides from their lipid conjugates after oral absorption [7]. Another potential limitation in peptide lipidization is efflux from intestinal epithelial cells via P-glycoprotein and multidrug resistance protein 2, which has been demonstrated with lipophilic cyclopeptides [8].

The challenges of bioavailability

The problems facing oral delivery of peptides and proteins have been approached from many different angles, several of which have claimed that an increase in GI absorption of peptides and proteins can be readily achieved. One might, therefore, ask why none of the technologies has yet been fully developed into an oral dosage form for peptide and protein drugs? The answer is that there are many other criteria that must be fulfilled to bring an oral peptide or protein drug to the market. For example, bioavailability is very low for most oral protein delivery systems. This might be acceptable for peptide drugs that are both cheap and safe, such as the oral dosage form for desmopressin, but low bioavailability implies a large variation in absorption and a high manufacturing cost, which are both unacceptable for the development of most peptide and protein drugs.

Even if a dosage form is developed to produce a reasonable bioavailability, reproducibility is another potential problem. For drugs such as insulin that have a relatively narrow therapeutic window, the effects on GI absorption of age, genomic factors, pathophysiological conditions and other individual variations must be carefully investigated. With some of the oral delivery technologies, an accurate prediction of bioavailability might prove to be very difficult. Finally, most peptide and protein drugs require chronic administration and hence the effects of long-term oral administration of absorption carriers on both the GI and systemic physiology must also be carefully evaluated.

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