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Research review paper

# A review of advanced oral drug delivery technologies facilitating the protection and absorption of protein and peptide molecules

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ABSTRACT

The oral delivery of proteins and peptides is a dynamic research field despite the numerous challenges limiting their effective delivery. Successful oral delivery of proteins and peptides requires the accomplishment of three key tasks: protection of the macromolecules from degradation in the gastrointestinal tract (GIT), permeation through the intestinal barrier and absorption of molecules into the systemic circulation. Currently, no clinically useful oral formulations have been developed but several attempts have been made to overcome the challenges of low oral bioavailability resulting from poor absorption, poor permeation and enzymatic degradation of the proteins and peptides in the GIT. Present strategies attempt to provide structural protection of the proteins and peptides and improved absorption through the use of enzyme inhibitors, absorption enhancers, novel polymeric delivery systems and chemical modification. However, each of these technologies has their limitations despite showing positive results. This review attempts to discuss the physical and chemical barriers of the GIT with particular emphasis on the current approaches employed to overcome these barriers, including the evaluation of other non-parenteral routes of protein and peptide delivery. In addition, this review assimilates oral formulation strategies under development and within the clinical trial stage in relation to their benefits and drawbacks with regard to facilitating optimal protection and absorption of proteins and peptides, as well as pertinent future challenges and opportunities governing oral drug delivery.



**Contents**



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## Introduction

The oral delivery of proteins and peptides, although a highly attractive approach, remains a significant challenge in drug delivery technology, as a result of their unfavorable physicochemical properties (Catnach et al., 1994; Hamman et al., 2005; Park et al., 2011). Administering drugs by the oral route is preferred due to its improved convenience and patient compliance (Brayden and O'Mahony, 1998; Park et al., 2011). However, oral drug delivery can be particularly challenging when considering the variations that occur in the absorption of a molecule due to interactions with gastric contents/secretions, membrane permeability, intestinal transit and gastric emptying. This is particularly with respect to the delivery of sensitive proteins and peptides (Marques et al., 2011). Therapeutic proteins and peptides are gaining increased popularity, owing to advances in biotechnology that enable them to be the molecules of choice for an assortment of diseases (Chin et al., 2012; Park et al., 2011). The high specificity and activity of proteins and peptides make them applicable for targeted delivery in clinical practice (Brayden and O'Mahony, 1998; Chin et al., 2012; Park et al., 2011). The new 2013 Pharmaceutical Research and Manufacturers of America (PhRMA) report on "Biologic Medicines in Development" identified over 900 protein and peptide-based medicines in development, targeting more than 100 diseases, of which 353 for cancer and related conditions, 187 for infectious diseases, 69 for autoimmune diseases and 59 for cardiovascular diseases. This significantly increases the demand and focus towards achieving effective and simple routes of delivering proteins and peptides via the oral route.

Conventionally, therapeutic proteins and peptides are administered intravenously, subcutaneously or intramuscularly since the oral route of administration may result in degradation in the gastrointestinal tract (GIT) (O' Connor, 2009; Schiffter, 2011). Although significant progress has been made towards the development of oral delivery systems for proteins and peptides, the field is limited by the low membrane permeability of these high molecular mass compounds, as well as their hydrophilicity, instability and rapid enzymatic degradation in the GIT (Camenich et al., 1998; Donovan et al., 1990; Park et al., 2011). Proposed technologies and approaches targeting the complications in the oral delivery of proteins and peptides although useful in some instances, nevertheless hold limitations that enable successful delivery (Park et al., 2011).

Therapeutic proteins and peptides have gained a significant market interest owing to their increased development and applicability to multiple disease conditions (Chin et al., 2012; Park et al., 2011). Consequently, advancements towards successful oral delivery of proteins and peptides through protection and increased absorption remain an active area of research and researchers have intensified their research towards achieving this goal (Chiasma Inc.; Cosmo Pharmaceuticals, Inc.; Diabetology Ltd.; Emisphere Technology, Inc.; Enteris BioPharma, Inc; Merrion Pharmaceuticals, Ltd.; Oramed Pharmaceuticals, Inc.; Proxima Concepts, Ltd; Tarsa Therapeutics, Inc.). This review article summarizes the major challenges facing oral protein and peptide delivery as well as the various attempts at overcoming these challenges. Current and new technologies within this dynamic field of research will be discussed, including the potential benefits of each technology and possible limitations that exist. Potential for improvement is a key focus in the development of new formulation strategies and technologies.

## The gastrointestinal barrier: a physical and chemical impediment to oral protein and peptide delivery

The GIT epithelium acts as a physical and chemical barrier towards the absorption of proteins and peptides (Antunes et al., 2013; Lee, 2002). The mucosal surface of the GIT is a large interface that is protected by a monolayer of epithelial cells, connected by tight junctions that provides an effective barrier against the absorption of proteins and peptides and thus, represents a physical gatekeeper that selectively restricts the entry of large molecules into the systemic circulation (Antunes et al., 2013; Neutra and Kraehenbuhl, 1993). Owing to the large molecular mass and hydrophilic properties of proteins and peptides, transport across the intestinal epithelium becomes extremely challenging (Lee, 2002). Nevertheless, studies have suggested that the transport of macromolecules across the intestinal epithelium is possible provided that there is minimal degradation of the protein or peptide molecule in the GIT through the use of permeation enhancers, physicochemical modification strategies and stimuli-responsive and mucoadhesive polymeric systems (Lundin and Vilhardt, 1986; Takaori et al., 1986; Walker et al., 1990).

### *The GIT as a physical barrier for protein and peptide absorption*

The possible mechanisms by which proteins and peptides are absorbed from the GIT include passive transport, active transport and endocytosis (Artursson et al., 2007; Potocky et al., 2003). The passive transport of molecules across the intestinal membrane occurs through simple or facilitated diffusion, along a concentration gradient, independent of chemical energy and principally dependent on the intrinsic physicochemical properties of the transported molecule, including its ability to diffuse across cellular barriers (Stein, 1986). The low lipophilicity and large molecular mass of proteins and peptides limit its absorption by this mechanism. However, it proves beneficial for the absorption of di/tripeptides (Catnach et al., 1994). In contrast, active transport of molecules is a process involving chemical expenditure, occurring against a concentration gradient for the transport of molecules across the GIT epithelium (Stein, 1986). Lastly, molecules may be transported through endocytosis which is an energy-consuming process involving the engulfment of molecules for absorption (Artursson et al., 2007; Potocky et al., 2003).

The pathways available for the potential transport of proteins and peptides through these mechanisms include the transcellular pathway and paracellular route as shown in Fig. 1 (Ménard et al., 2012). The transcellular pathway involves the transport of molecules across cells which can take place either by passive diffusion, a specific carrier or through transcytosis and receptor-mediated endocytosis (Ménard et al., 2012). Transcellular passive diffusion is dependent on the physico-chemical properties of the molecule such as size, charge and lipophilicity in order to facilitate the passive flux of molecules through the lipophilic, apical and basolateral membranes of the intestinal epithelium (Liu et al., 2009). Molecules may also be absorbed transcellularly using specific carriers such as peptide and amino acid transporters that transport molecules such as from the intestinal lumen into the cell (Antunes et al., 2013; Liu et al., 2009).

Intact di- and tripeptides can be actively transported for absorption in the small intestine by specific carrier systems, distinctive from the