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Intestinal permeation enhancers for oral peptide delivery☆

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ABSTRACT

Intestinal permeation enhancers (PEs) are one of the most widely tested strategies to improve oral delivery of therapeutic peptides. This article assesses the intestinal permeation enhancement action of over 250 PEs that have been tested in intestinal delivery models. In depth analysis of pre-clinical data is presented for PEs as components of proprietary delivery systems that have progressed to clinical trials. Given the importance of co-presentation of sufficiently high concentrations of PE and peptide at the small intestinal epithelium, there is an emphasis on studies where PEs have been formulated with poorly permeable molecules in solid dosage forms and lipoidal dispersions.

Contents

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1. Introduction

Growth in global peptide markets has spurred development of technologies that enable oral delivery of poorly permeable drugs. Initial delivery strategies focused on inclusion of candidate excipients that protected the peptide from intestinal degradation and transiently altered intestinal permeability [1]. The majority of oral peptide delivery technologies that are currently in clinical trials use formulations with established intestinal PEs that have a history of safe use in man [2]. Recent clinical data suggests that inclusion of PEs in oral formulations can safely assist absorption of selected potent peptides with a large therapeutic index. For example, primary endpoints were met in a Phase III trial of octreotide formulated in an oily suspension with a medium chain fatty acid salt, sodium caprylate (C_8) [3]. In parallel, a new generation of PEs with more specific mechanisms of action are in preclinical research, and may confer improved safety and efficacy over those currently in development. This article summarises the progress of ~250 PEs that have been tested in preclinical intestinal delivery models (Tables 1, S1). An in-depth review of pre-clinical data is presented for PEs in proprietary delivery systems that have progressed to clinical development. The review by Aguirre *et al.* (this Issue [4]) evaluates the performance of technologies in clinical trials, of which most are enteric-coated solid dosage forms containing PEs. We focus here on how PEs alter intestinal permeability and on innovations that may further assist translation of safety and efficacy outcomes from pre-clinical models to man.

2. Therapeutic peptides

A drug delivery system that facilitates oral peptide administration has long been desired. There are ~55 therapeutic peptides marketed as parenteral formulations (based on a ~9 kDa cut-off in molecular weight (MW)) (Table 2) and a further 140 in clinical development [5]. Compared to small molecules, peptides are attractive due to their specificity, potency, efficacy, and low toxicity. Clinical potential of unmodified injectable peptides can be hampered by a short plasma half-life ($t_{1/2}$) due to labile moieties and higher manufacturing costs relative to small molecules. A breakdown of marketed peptide products indicates that injection routes (61%) are the most common, followed by topical (11%), nasal (9%), oral (9%) and ophthalmic (4%), noting that bioavailability is typically low and variable from non-injectable routes [6].

Injection requirements are associated with lack of adherence to dosing regimens, hence the impetus towards long acting formulations that are administered less often. Thus, for glucagon-like-Peptide 1 (GLP-1) analogues, sub-cutaneous (s.c.) injection of exenatide has shifted from twice-a-day administration (Byetta®; Lilly, USA) to once weekly administration (*e.g.* Bydureon®, Lilly). This was achieved by development of a microsphere-based controlled release system [7], whereas competing approaches have attempted to improve stability and reduce recognition by the reticuloendothelial system by conjugating lipid moieties to amino acid residues or by fusing the analogue to albumen. Although needle fabrication technology has improved in the last 20 years, injections are still inconvenient in the longer term and can delay take-up and adherence to regimes necessitated by chronic diseases. In the case of type 2 diabetes (T2D), early initiation of insulin can slow the progressive destruction of pancreatic β-cells [8], but T2D patients frequently require dose adjustments related to peripheral hypoglycaemia [9]. Oral insulin may reduce such risks because it is absorbed via the portal vein and therefore imitates pancreatic secretion to the liver [10]. This can also reduce two other side effects attributed to s.c. insulin in the periphery: weight gain and lipodystrophy [11].

An oral peptide dosage form would likely reduce costs associated with sterile manufacture of injectables, cold chain, needle disposal, and staff/patient training, but these savings would be offset against the requirement for higher doses compared to injection. A commercial driver for oral peptides is life cycle extension and increased revenue from branded medicines based around new patents. Development of oral delivery systems for approved injectable peptides has the benefit of known pharmacology for the active pharmaceutical ingredient (API), good safety profiles (at least for the injected route) and established analytical detection methods. The most clinically-advanced oral peptide formulations are being developed for diabetes (insulin, GLP-1 analogues), osteoporosis (salmon calcitonin, sCT; teriparatide (PTH 1–34)), and acromegaly (octreotide). Anti-diabetic peptides account for ~40% of peptides in commercial oral peptide delivery programmes and Table S2 details selected patents filed on oral insulin over the last 30 years. Synthesis of injectable anti-diabetic peptides with long plasma $t_{1/2}$ values is also contributing to investment in oral peptide delivery systems (*e.g.* $t_{1/2}$ = 160 h for the GLP-1 analogue, semaglutide, Novo-Nordisk, Denmark [12]), as they may yield better oral pharmacokinetic (PK) data than short-acting counterparts. Competition between GLP-1 analogues makes oral formulation a key battleground [5].

Development of non-injected dosage forms has had some commercial successes, including oral desmopressin (DDAVP®, Ferring, Switzerland), oral cyclosporin (Neoral®, Novartis, Switzerland) and nasal calcitonin (Miacalcin®, Novartis). The suitability of commercially available peptides for oral reformulation depends on their physicochemical properties (MW, solubility), chemical complexity, therapeutic considerations (route/frequency of administration, therapeutic index) and cost-effectiveness. Peptides typically exhibit high aqueous solubility and low permeability, properties that unofficially place them in the Biopharmaceutics Classification system (BCS) Class III. Nevertheless, some peptides with cationic and anionic functional groups exhibit complicated pH-dependent solubility, where solubility is high in acidic conditions at pH values below their isoelectric point (pI), and is relatively low at pH values at and above their pI. Many basic molecules rely on acid/base phenomena for dissolution within the stomach and subsequent absorption across the duodenum and jejunum, so peptides with low intrinsic solubility are problematic. For example, insulin dissolves in dilute acid but not at neutral pH, which could manifest as poor dissolution in the small intestine. Peptides that have a MW >6000 Da do not have any appreciable intestinal permeability when delivered orally, this makes insulin (5808 Da) especially challenging, with difficulty decreasing in the order of teriparatide (4118 Da) > exenatide (4187 Da) > sCT (3532 Da) > octreotide (1019 Da). In addition, there is a correlation between MW and susceptibility to proteolysis [13].

An ideal oral candidate peptide should therefore have a low MW, high potency, enzymatic/chemical stability (*e.g.* cyclised peptides, D-substituted amino acids), a high therapeutic index and be of relatively low cost to synthesise. Desmopressin (MW 1069 Da) contains stable amino acids; it has an oral bioavailability (F) of only 0.17%, so high potency is its key attribute [14]. Prandial insulin is more challenging because it requires three relatively high mealtime doses to reach the required plasma levels per day. The s.c. insulin dose required for management of Type 1 diabetes (T1D) of 0.5–0.8 IU/kg per dose (1.2–1.9 mg); if normalised for an oral system designed for an oral F of 10%–20%, a dose level of 6–20 mg would be required. A recent oral insulin clinical study included 8 mg (240 IU) insulin three times daily [15], whereas