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Review article

Novel strategies in the oral delivery of antidiabetic peptide drugs – Insulin, GLP 1 and its analogs

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ABSTRACT

As diabetes is a complex disorder being a major cause of mortality and morbidity in epidemic rates, continuous research has been done on new drug types and administration routes. Up to now, a large number of therapeutic peptides have been produced to treat diabetes including insulin, glucagon-like peptide-1 (GLP-1) and its analogs. The most common route of administration of these antidiabetic peptides is parenteral. Due to several drawbacks associated with this invasive route, delivery of these antidiabetic peptides by the oral route has been a goal of pharmaceutical technology for many decades. Dosage form development should focus on overcoming the limitations facing oral peptides delivery as degradation by proteolytic enzymes and poor absorption in the gastrointestinal tract (GIT). This review focuses on currently developed strategies to improve oral bioavailability of these peptide based drugs; evaluating their advantages and limitations in addition to discussing future perspectives on oral peptides delivery. Depending on the previous reports and papers, the area of nanocarriers systems including polymeric nanoparticles, solid lipid nanoparticles, liposomes and micelles seem to be the most promising strategy that could be applied for successful oral peptides delivery; but still further potential attempts are required to be able to achieve the FDA approved oral antidiabetic peptide delivery system.

Contents

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1. Introduction

Proteins and peptides are the building blocks of life and are now evolving as a very promising brand of therapeutic drugs [1]. They have gained much interest because they can be used for the treatment of several diseases due to their ability to provide effective and potent action [2–4]. More than that, peptides and proteins are highly selective [5] that can lead to a significant decline in toxicity. "Diseases that might be treated with this type of therapeutics include auto immune diseases, cancer, mental disorder, hypertension, and certain cardiovascular and metabolic diseases" [6]. A wide variety of peptide and protein drugs is now developed as a result of advances in the biotechnology field [7].

Diabetes mellitus is an endocrinological and/or metabolic disorder [8], and the worldwide prevalence and incidence of it has continued to increase dramatically. Currently, more than 250 million people in the world have diabetes and it is predicted that this number will double over 20 years [9]. The disease results in hyperglycemia which may cause multi-organ damage. The debilitating effects of diabetes mellitus include various organ failures, progressive metabolic complications such as retinopathy, nephropathy, and/or neuropathy [9–11]. The main aim for the treatment of type I and type II diabetes is to cure the symptoms related to hyperglycemia [12].

Over the last years, the interest of the pharmaceutical technology utilizing therapeutic peptides in diabetes treatment has been increased. However, these peptide drugs have several drawbacks, including low bioavailability, metabolic liability and short half-lives [13–15]. Hence, these drugs are usually administered by parenteral route [16–18]. However, since injections are associated with pain and low patient compliance [19], researchers in the pharmaceutical technology field believe that alternative routes of non-invasively delivery ways such the oral, pulmonary, nasal, transdermal and buccal routes are highly desirable for peptides and proteins delivery [20–22]. Among these non-invasive routes, the oral route is often the most preferred route.

2. Delivery of the most common antidiabetic peptides

2.1. Insulin

Insulin is a life-saving drug for diabetes as it has the ability to control the blood glucose level by facilitating the uptake of glucose [23]. Until now, insulin is the first line treatment of type 1 diabetes. It is also used to treat type 2 diabetic patients (especially in late-stage disease) [24]. Human insulin is consisted of two amino acid chains: A chain (21 amino acid residues) and B chain (30 amino acid residues) linked by disulfide bonds. Insulin can be isolated from human, porcine, bovine or sheep sources [25]. Currently; insulin is still administered by subcutaneous injection because of its instability in the gastrointestinal route, due to stomach acid and proteolytic enzymes present in the intestine, and low permeability through the intestinal mucosa [26] in addition to the hepatic first pass effect [27].

However, multiple daily insulin injections can lead to infection at the injection site in addition to psychological stress leading to poor patient compliance [26,28], and as a result non-effective treatment.

All of these drawbacks have motivated researchers to develop a safe and effective noninvasive route for insulin delivery. Among different noninvasive routes, oral insulin delivery not only improves the quality of life of diabetes patients who routinely receive insulin by the subcutaneous route, but also offers many advantages: rapid hepatic insulinisation in addition to avoidance of peripheral hyperinsulinemia and other adverse effects such as possible hypoglycemia and weight gain [29,30].

2.2. Glucagon-like peptide-1 and its analogs

The incretin hormone glucagon-like peptide-1(GLP-1) is a 30 amino-acid peptide derived from a proglucagon gene that is secreted by neuroendocrine L cells of the ilium and colon [31]. Food intake is the primary physiological stimulus of GLP-1 release from enter-endocrine cells [32]. The main effect of incretins is the reduction of blood glucose, mediated by the regulation of hormonal pancreatic secretions, inhibiting gastric emptying and reducing appetite and food intake [33]. The half-life of bioactive GLP-1 in the circulation is less than 2 min due to rapid inactivation by the ubiquitously expressed dipeptidyl peptidase-4 (DPP-4) which is mainly located on the luminal surface of the endothelial cells [31]. To overcome premature GLP-1 metabolism, long-acting GLP-1 analogs have been developed to resist DPP-4 degradation. Currently, six glucagon-like peptide-1 receptor agonists (GLP-1RAs) are approved for treating type 2 diabetes. These fall into two classes based on their receptor activation: short-acting exenatide twice daily and lixisenatide once daily, and longer-acting liraglutide once daily, exenatide once weekly, albiglutide once weekly and dulaglutide once weekly [34].

Both exenatide and liraglutide are delivered parenterally and have been proven to improve glycemic control. Therefore an oral route is preferable as it could prove safe and effective, it would mimic physiological route of GLP-1 from intestine to circulation to avoid potential side effects, and provide more convenience, ease of administration, and comfort, which would increase patients' compliance to the treatment and thus increase the treatment efficacy [35,37].

3. Major obstacles associated with oral delivery of therapeutic peptides

Peptides and proteins could be transported across the GIT epithelium via either transcellular or paracellular pathway. However, these molecules are hydrophilic with large size. So, they would not be expected to follow the transcellular route of absorption by means of passive diffusion. Alternatively, the paracellular route is an aqueous extracellular route that may be interesting for peptides and proteins delivery due to possible deficiency in proteolytic enzymes. It was demonstrated that the paracellular route is not an option for absorption of proteins and peptides because they cannot fit in these spaces [38–40]. Another major obstacle that contributes to the extremely low bioavailability of proteins and peptides is the presystemic enzymatic degradation in the harsh environment of the GI tract as well as presystemic elimination in the liver [38–42]. Besides, efflux transporters such as P-glycoprotein (P-gp), a 170-kDa protein, might contribute significantly to the poor bioavailability of peptides and proteins [43,44] as this protein acts in reverse to transcellular drug absorption [45,46].

Thus, the barriers that limit oral peptide delivery can be summarized as follow:

- Low pH environment of the gastric media.
- Enzymatic barrier.
- Viscous mucous layer.
- The intestinal epithelium cells.

As the possibilities in their oral delivery and the main challenges in their development, current and future prospects, with focus on technology trends in the market has been summarized