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Oral protein delivery: Current status and future prospect

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ABSTRACT

Advances in biotechnology have produced therapeutically active proteins on a commercial scale, and therapeutic proteins are now extensively applied in medical practices to treat various diseases. Oral delivery of protein drugs is a highly attractive approach, and, naturally, numerous attempts have been made to develop such formulations. Despite various attempts, however, no clinically useful oral formulations have been developed, and this is mainly due to extremely low bioavailability of protein drugs. The effective oral protein delivery needs to overcome barriers related to poor absorption, poor permeation, and degradation in the gastrointestinal tract. Various strategies have been explored for enhancing the bioavailability of orally administered proteins. They include chemical modification of protein drugs, use of enzyme inhibitors, and exploration of special formulation ingredients, such as absorption enhancers and mucoadhesive polymers. This article examines the current technologies under development for oral protein delivery.

1. Introduction

Each year new therapeutic proteins are introduced into the market. Advances in biotechnology have accelerated the economical, large-scale production of proteins, vaccines, and hormones, making them readily available for therapeutic applications in medical practices and clinical studies. Therapeutic proteins have become the drugs of choice for treating numerous diseases due to their exquisite specificity and bioactivity.

Administering drugs by oral route is preferred to any other routes because of its simplicity and convenience. Oral administration of protein drugs, however, is extremely difficult due to their extremely low bioavailability. Development of oral protein formulations requires overcoming obstacles, such as low permeability of large molecules [1], lack of lipophilicity [2], and inactivation or rapid enzymatic degradation in the gastrointestinal (GI) tract [3]. These unfavorable physicochemical properties of proteins present monumental challenges to pharmaceutical formulation scientists.

The objective of this article is to review the general approaches that have been used to improve bioavailability of orally delivered proteins by overcoming various physiological barriers, and to provide the information on oral protein delivery technologies currently under investigation.

2. Main approaches used for oral protein delivery

Through the years, various strategies have been tried for improving bioavailability of therapeutic proteins. The approaches commonly used in formulating oral protein delivery systems include using specific excipients, such as absorption enhancers, enzyme inhibitors, and mucoadhesive polymers, and using formulations allowing protection of protein drugs from the harsh environment in the GI tract, as listed in Table 1.

2.1. Absorption enhancers

To improve the permeation of protein drugs through the intestinal wall, absorption enhancers have been used as formulation components, which include detergents, surfactants, bile salts, and Ca^{2+}-chelating agents [4,5]. Detergents or surfactants enhance the transcellular transport by disrupting the lipid bilayer, rendering the cell membrane more permeable [6]. Chelating agents form complexes with calcium ions and rupture tight junctions to facilitate paracellular transport of proteins. Long alkyl chain enhancers, including fatty acid sodium caprate and acyl carnitines, have shown similarly improved absorption via transient opening of tight junctions [7,8]. Zonula Occludens toxin is known to be a safe and effective enhancer, altering intestinal epithelia tight junctions transiently for passage of macromolecules, such as insulin, through mucosal barriers [9].

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Table 1
Approaches used in oral protein formulations.

Approaches	Systems	Outcomes for absorption	Drawbacks
Absorption enhancers	Bile salts, fatty acids, surfactants, salicylates, chelators, zonular occludens toxin	Increase membrane permeation	Available transport of both protein/peptide drugs and undesirable molecules present in GIT
Enzyme inhibitors	Sodium glycocholate, camostat mesilate, bacitracin, soybean trypsin inhibitor, aprotinin, CkOVM, DkOVM, polymer–inhibitor conjugates	Resist enzyme degradation present in stomach and intestine	Available inducing severe side effects in chronic therapy
Mucoadhesive polymers	P(MAA-g-EG) hydrogel microparticles, lectin-conjugated alginate microparticles, thiolated polymers Gastrointestinal mucoadhesive patch system	Site-specific delivery and improve membrane permeation	Limitation due to the natural mucus turnover in intestine
	Mucoadhesive polymer–inhibitor conjugates	Site-specific drug delivery and resist enzyme degradation	Limitation due to the extensive costs of certain enzyme inhibitors
Formulation vehicles	Emulsions –S/O/W emulsion –O/W emulsion –Enteric-coated O/W emulsion	Protect drug from acid and luminal proteases in the GIT and enhance permeation through intestinal mucosa	Physicochemical instability in long-term storage and requirement for storage at low temperatures
	Liposomes –Double liposomes –Fusogenic liposomes –Crosslinked liposomes	Improve physical stability and increase membrane permeation	Low stability of liposomes
	Microspheres –Eudragit S100 microspheres –pH-sensitive P(MAA-g-EG) microspheres	Prevent proteolytic degradation in stomach and upper portion of small intestine. Restrict release of drug to favorable area of GIT	Concerns of protein stability during processing, release and storage
	Nanoparticles –PMAA/chitosan/PEG nanoparticles –Polystyrene/chitosan/PLA–PEG nanoparticles	Prevent enzymatic degradation and increase intestinal epithelial absorption	Low loading efficiency of hydrophilic drugs, difficulty of precise size control and avoidance of particle aggregation

Abbreviations: CkOVM, chicken ovomucoid; DkOVM, duck ovomucoid; S/O/W, solid-in-oil-in-water; P(MAA-g-EG), poly(methacrylic acid-g-ethylene glycol); PEG, Poly(ethylene glycol); PLA, poly(lactic acid); GIT, gastrointestinal tract.

Co-administration of proteins with carrier molecules can enhance bioavailability of proteins [10–13]. For example, lipophilic carrier enhancers facilitated the absorption of proteins, such as insulin [13,14], human growth hormone [12,15], calcitonin [16], and recombinant parathyroid hormone (rPTH) [11]. Carrier molecules temporarily stabilize the partially unfolded conformations of proteins exposing their hydrophobic side chains. Thus, the carrier molecules altered lipid solubility, allowing them to gain access to pores of integral membrane transporter. This result in enhanced absorption through lipid bilayers [17]. It is noted, however, that the use of these absorption enhancers is able to enhance the transport of not only proteins but also undesirable molecules present in the GI tract when cell membranes are permeabilized or tight junctions opened [18].

2.2. Enzyme inhibitors

One of main barriers in oral protein delivery is that proteins can be rapidly degraded by various proteolytic enzymes. To minimize degradation of proteins by various proteolytic enzymes, researchers have used trypsin or α-chymotrypsin inhibitors, such as pancreatic inhibitor [19], soybean trypsin inhibitor [19], FK-448 [20], camostat mesylate [21], and aprotinin [22]. As new class of enzyme inhibitors, chicken and duck ovomucoids have been recently identified [23,24]. For example, a formulation containing insulin and duck ovomucoid offered 100% protection against trypsin- or α-chymotrypsin-mediated insulin degradation. Polymer–inhibitor conjugates such as carboxymethylcellulose–Bowman Birk inhibitor and carboxymethylcellulose–elastinal (CMC–Ela) have offered in vitro protection against trypsin, α-chymotrypsin and elastase [25]. In particular, CMC–Ela displayed higher inhibitory activity toward elastase that nearly 33% of therapeutic agent remained stable against enzymatic attack even after 4 h of incubation. However, protease inhibitors can influence the absorption of other proteins and induce severe toxic effects during chronic drug therapy.

2.3. Mucoadhesive polymeric systems

Stimuli responsive and mucoadhesive polymeric systems have been of great interest as protein delivery carriers because they exhibit dramatic changes in network structure or swelling behavior in response to changes in environmental factors, such as pH, temperature, enzymes, light, electric field or ionic strength [26].

Mucoadhesive polymeric systems could extend the residence time at the site of drug absorption. They maintain intimate contacts with the mucus to increase the drug concentration gradient and ensure immediate absorption without dilution or degradation in the luminal fluid [27,28]. The mucoadhesive controlled release systems can be designed for simultaneous release of both drug and inhibitor, allowing proteins to be efficiently protected [29]. The pH-sensitive mucoadhesive polymeric carriers have been used to protect the protein drugs from proteolytic degradation in the stomach as well as in the upper portion of the small intestine. For instance, poly(methacrylic acid-g-ethylene glycol) [P(MAA-g-EG)] exhibits pH-dependent swelling behavior resulting from the formation or dissociation of interpolymer complexes [30,31]. The polymeric microparticles loaded with insulin showed a rapid burst release with high insulin absorption in the intestine, resulting in a greater hypoglycemic effect without detectable mucosal damage [32]. P(MAA-g-EG) hydrogels showed very high (~10%) pharmacological availability of orally given insulin [33,34].

Thiolated polymers (thiomers), mucoadhesive-based polymers with thiol-bearing side chains, have been considered as a promising alternative in non-invasive protein delivery. Their strong mucoadhesive properties are due to additional covalent bonds between thiol groups of thiomers and cysteine-rich subdomains of mucus glycoproteins [35]. Orally administered thiomer-based insulin tablets could significantly decrease blood glucose levels for 24 h as compared with subcutaneous injections [36]. However, the adhesion properties of thiomers might be changed because the natural mucus turnover in the human intestine is in the range of 12–24 h [37]. Thus, the limited adhesion of thiomers to the mucus