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Review on Novel Approaches for Oral Protein and Peptide Drug Delivery

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ABSTRACT

Convenient oral administration of protein and peptide drugs remains a significant challenge due to their susceptibility to degradation in the gastrointestinal [GI] tract and limited permeability. This review explores the physicochemical properties of these biologics, including molecular structure, solubility, and stability under various conditions, which critically impact their therapeutic potential. Advances in oral drug delivery systems, such as nanoparticle-based carriers, lipid-based formulations like liposomes and micelles, and innovative polymer technologies, are discussed as pivotal strategies to protect these sensitive molecules and enhance absorption.

Key approaches for improving stability and bioavailability include the use of protease inhibitors, encapsulation techniques, and chemical modifications tailored for GI uptake. Promising strategies such as permeation enhancers, peptide transporters, and bile salts are identified as significant contributors to overcoming absorption barriers. The potential of nanotechnology to enhance penetration and targeted delivery is also emphasized.

The review further examines formulation challenges, including peptide aggregation and the comparative advantages of liquid, tablet, and capsule dosage forms. It highlights strategies for achieving targeted and controlled drug release within the GI tract, ensuring optimized therapeutic outcomes. Finally, critical considerations surrounding clinical trial design, pharmacokinetics, and regulatory pathways for the commercialization of oral biologics are addressed, offering insights into the translation of innovative technologies into effective patient therapies.

Keywords: Oral drug delivery, Protein therapeutics, Peptide drugs, Permeation enhancers, Gastro-intestinal targeting, Personalized medicine.

1. Introduction to Oral Delivery of Protein and Peptide Drugs:

1.1 Overview of Protein and Peptide Therapeutics

The treatment of numerous ailments, such as cancer, autoimmune diseases, and even metabolic disorders like diabetes, has been completely transformed by protein and peptide therapy. These biopharmaceuticals include growth factors, peptide hormones, and monoclonal antibodies, and they target disease pathways at the molecular level. They are highly effective and selective. For instance, insulin has been the mainstay in the treatment of diabetes, whereas newer therapies such as GLP-1 agonists present new avenues in metabolic control [1]. Protein and peptide drugs have been witnessing a tremendous increase in market due to advancements in biotechnology. New products are being launched in the market every year. The clinical efficacy of these therapeutics is often hindered by the route of administration, which currently remains injectable.

1.2 Oral Bioavailability Challenges

Oral delivery of protein and peptide drugs remains a challenge because of various physiological and biochemical barriers. Enzymes, particularly proteases and peptidases, which break proteins and peptides into smaller fragments that are inactive or cannot be absorbed, are prone to breaking down such big molecules in the GI tract [2].The stomach's acidic pH and intestinal mucosal barriers also provide significant impediments to absorption. As a result, only a portion of the oral dose can enter the bloodstream in its active state, resulting in reduced systemic bioavailability [3]. To increase the oral bioavailability of protein and peptide medications, numerous approaches have been devised. These include enzyme inhibitors, absorption boosters, and novel delivery vehicles including hydrogels, liposomes, and nanoparticles that help the medication pass through the intestinal wall and prevent degradation [4]. That being said, no oral formulation has been created thus far that can consistently produce therapeutic results more quickly or effectively than injectable formulations.

1.3 Importance and Need for Oral Formulations

Oral protein and peptide medication formulations are essential for enhancing patient adherence, convenience, and general health outcomes. Compared to injections, oral delivery has a number of benefits, including as simplicity, self-administration, and the elimination of the need for medical assistance in administering the medication. These advantages make oral formulations particularly attractive for chronic conditions that require long-term treatment, such as diabetes and hormonal imbalances [5]. Adherence to injectable therapy may be substantially lower than that of oral treatments, mainly because of the pain and hassle involved in injections [6].Additionally, reducing hospital stays and the need for trained staff to administer parenteral medications can reduce healthcare costs. Therefore, creating effective oral formulations can enhance the patient's quality of life and lessen the overall strain on the healthcare system [7]. This demand for oral protein and peptide drug formulations will be driven primarily by the increasing number of patients who look for non-invasive alternatives as biopharmaceutical companies continue to discover new ways around the barriers to oral bioavailability. The development of these oral drug delivery systems will continue, culminating in a high value upon being presented to the patient: effective, accessible, and cost-effective therapeutic options.

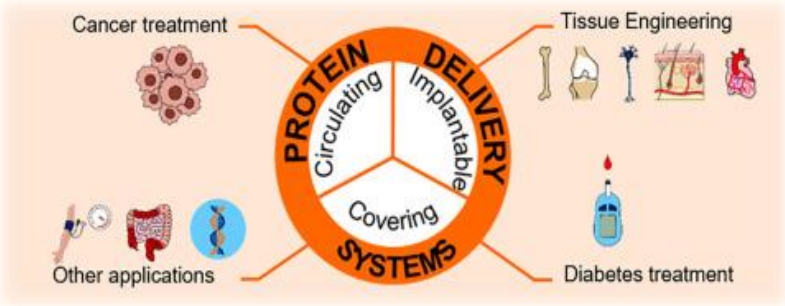

Figure 1. The various applications of PPDS [63]

2. Physicochemical Properties of Proteins and Peptides

The discovery of protein and peptide therapeutics is one of the greatest revolutions in modern medicine, where targeted treatments were devised for seemingly inaccessible conditions, such as certain viruses and autoimmune disorders. However, despite their seemingly promising therapeutical potential, their physicochemical properties greatly influence both the design of formulation and stability and delivery. Knowing their molecular structure, solubility, permeability, and sensitivity to environmental effects is important for the optimization of their efficacy.

2.1 Molecular Structure and Stability

The molecular structure of proteins and peptides determines their biological function and therapeutic potential. Proteins and peptides are composed of amino acid sequences folded into specific three-dimensional structures, which are important for their biological activity. These molecules depend mainly on secondary, tertiary, and quaternary structures for stability. Their therapeutic efficacy is compromised because these structures get denatured or aggregate through temperature fluctuations, chemical modifications, or mechanical stresses [8].

Ionic strength, pH, and stabilizing agents, for example, have been found to influence the stability of proteins and peptides physicochemically. For instance, some proteins are very sensitive to environmental conditions and can be misfolded or aggregate;

such proteins have lower efficacy or may even provoke an immune response in patients upon injection. Formulations containing excipients such as sugars and salts may stabilize proteins, thus avoiding degradation during storage or transit within the body [9].

2.2 Solubility and Permeability Issues

Solubility is the most important property that determines the bioavailability of protein and peptide therapeutics. These large, complex molecules are generally very poorly soluble in aqueous conditions, particularly at the physiological pH. This condition of poor solubility becomes worse when they also lack sufficient permeability across biological membranes. Such problems can be addressed by the formulation techniques that may combine different approaches. This may involve a solubilizer, nanoparticle, or encapsulation in a liposome. Such approaches are not only making proteins and peptides more soluble but also have the effect of increasing their oral absorption from the gastrointestinal tract. [10].

Furthermore, upon oral delivery through the gastrointestinal [GI] tract, peptides and proteins frequently encounter low permeability problems. Human guts possess a variety of digestive enzymes and harsh physiological conditions such as acidity and bile salts that can easily degrade proteins and peptides before they are absorbed into the body. This implies, although proteins and peptides exhibit very high specificity and potency, their low oral bioavailability remains a major challenge to their extensive clinical use. These are usually added in combination with enzyme inhibitors to oral formulations to improve bioavailability [11].

2.3 pH and Environmental Conditions Affecting Drug Stability

Proteins and peptides stability is highly dependent on environmental conditions, especially the pH. Alterations in pH trigger the conformation changes in proteins. These conformation changes then cause instability and altered functionality of these proteins. For example, a protein that has been engineered to be stable in a neutral pH condition might become denatured or aggregated in an acidic or basic environment and consequently lose activity. Furthermore, proteins and peptides are often designed to be stable in a physiological pH environment for easy delivery within the human body [12].

For instance, environmental factors such as temperature and light exposure influence the stability of protein and peptide drugs. High temperature accelerates degradation processes that involve hydrolysis and oxidation, such that in the peptide chain degradation is attained or undesirable aggregates are formed. The same is what can happen when light exposure occurs: free radicals are formed.

Given these sensitivities to environmental conditions, formulation strategies often focus on optimizing storage conditions such as refrigerated temperatures, avoidances of exposure to light, and stabilization by the use of cryo-protectants or lyophilisation [13, 14].

3. Barriers to Oral Delivery of Protein and Peptide Drugs

Although there is increasing interest in protein and peptide therapeutics, primarily because of their specificity and efficacy, the major challenge associated with their oral administration is their degradation in the GI tract by enzymes, pH variations, permeability issues with the membrane, and first-pass metabolism. This review aims to provide an overview of the key gastrointestinal barriers encountered by proteins and peptides, especially focusing on enzymatic degradation and pH variation.

3.1 Gastrointestinal Barriers: Enzymatic Degradation and pH Variation

Proteins and peptides are large molecules that are prone to enzymatic degradation in the gastrointestinal tract. The GI tract contains a variety of proteolytic enzymes, such as pepsin in the stomach and trypsin and chymotrypsin in the small intestine, that break down protein and peptide molecules into smaller fragments or amino acids, rendering them inactive [15]. This enzymatic degradation is one of the primary barriers to the oral delivery of proteins and peptides.

Additionally, the pH variation along the GI tract plays an important role in drug stability and absorption. The acidic pH of the stomach [about 1-2] can denature proteins and peptides, thus causing a disruption in their secondary and tertiary structures, leading to a loss of biological activity [16]. In contrast, the small intestine has a more neutral pH. However, the pH change from an acidic to a basic condition can be so drastic that it also impacts the stability of protein and peptide drugs. Thus, oral formulation development becomes a challenge because they have to resist these harsh conditions but still retain their therapeutic efficacy.

3.2 Challenges in Membrane Permeability

Even though proteins and peptides are stable in the stomach, their high molecular weight and hydrophilic nature make them poorly permeable to the intestinal membrane, which is a significant barrier for oral bioavailability. The intestinal epithelial cells form a tight junction that prevents large molecules from passing through easily [17]. Proteins and peptides have to cross the intestinal

mucosa into the bloodstream to be absorbed efficiently, but because of their size, they are unable to diffuse freely across the lipid bilayer of the intestinal cells.

Besides size-related problems, transporters in the gut can assist or hinder the absorption process. Many transporters could be exploited to promote drug delivery. However, it is usually inadequate for larger bio-molecules, such as proteins and peptides, and thus it is a problem of increasing their permeability either by adjustment of the formulation of the drug or by making use of enhancers of absorption such as surfactants, chitosan, or liposomes [18].

3.3 First-pass metabolism and its effects

Once absorbed through the intestinal wall, proteins and peptides undergo significant first-pass metabolism in the liver, where they are further broken down by enzymes, thereby reducing their systemic bioavailability [19]. The liver has a whole range of enzymes, including cytochrome P450, that are designed to metabolize foreign substances, including proteins and peptides. This metabolic degradation occurs before the drug enters systemic circulation, thus reducing the amount of the active drug available for action.

The primary determinant of the overall bioavailability of orally administered proteins and peptides is first-pass metabolism. Though the liver's metabolic activity prevents the absorption of harmful substances in the body, it causes loss of the substantial amount of administered dose. Therefore, it requires strategies that decrease first-pass metabolism, such as enzyme inhibitors or ways of formulating the drug that bypass the liver to enter the bloodstream more directly [20].

4. Advances in Oral Delivery Systems for Protein and Peptide Drugs

The therapeutic efficacy of proteins and peptides has found significant recognition, mainly in the treatments of chronic diseases, cancers, and metabolic disorders. Unfortunately, their oral administration as biopharmaceuticals is hindered by a number of physiological barriers, including enzymatic degradation in the GI tract, low aqueous solubility, poor membrane permeability, and extensive first-pass metabolism in the liver. Consequently, many sophisticated oral delivery systems have been engineered to overcome such problems and enhance the oral bioavailability of proteins and peptides. Such innovations comprise nanoparticle-based carriers, lipid-based systems, and polymer-based drug delivery technologies.

4.1 Nanoparticle-based Carriers

Nanoparticles have become one of the most promising approaches for the oral delivery of proteins and peptides. These particles range in size from 10 to 1000 nm and are made from biocompatible materials, such as lipids, polymers, or inorganic compounds. Their small size and surface properties make them excellent candidates for protecting protein and peptide drugs from enzymatic degradation in the gastrointestinal tract, a significant challenge to oral administration [21]. By encapsulating the therapeutic proteins or peptides within nanoparticles, they are protected from proteolytic enzymes such as pepsin, trypsin, and chymotrypsin that naturally degrade large molecules into inactive forms.

More importantly, nanoparticles enhance the solubility and stability of proteins and peptides. Proteins are in themselves hydrophilic in nature. Therefore, they are not very efficiently soluble in aqueous solutions. The nanoparticles improve their solubility in either a hydrophobic core that encapsulates the drugs or through surfactants that have better properties to be dissolved in the GI tract. Nanoparticles not only help the drug to reach systemic circulation more effectively but also support translocation of nanoparticles across the intestinal epithelium due to endocytosis, a process wherein cells engulf and internalize nanoparticles [22].

Engineering also includes surface modifications of nanoparticles. For instance, specific ligands, antibodies, or peptides conjugated to the nanoparticle's surface can facilitate targeting specific receptors or cells within the body; this would thereby enhance the therapeutic effect while avoiding off-target side effects. Thus, nanoparticles stand out as suitable for targeted therapy, such as in cancer treatments or metabolic disorders [23].

4.2 Lipid-based Systems: Liposomes, Micelles, and Solid Lipid Nanoparticles

Lipid-based drug delivery systems are another innovative route to improving the oral bioavailability of protein and peptide drugs: liposomes, micelles, and solid lipid nanoparticles [SLNs], in which natural biocompatibility and biodegradability of lipids offer a route for enhanced drug delivery and GI tract stabilization.

Like figure1, we can see that, Liposomes are spherical vesicles that contain drug mixtures in a bilayer matrix consisting of phospholipids. They can encapsulate hydrophilic and hydrophobic drugs. Because of their lipid nature, liposomes can protect proteins and peptides from digestive enzymes in the stomach environment and stabilize them. Liposomes can further be engineered

such that they enable the better drug release when deposited inside the small intestine, as it aids its absorption. Other than that, liposomes enable improving the protein-based therapeutics' solubility by augmenting the available surface area so that the medium for the proper release of a drug is preferably large [24].

However, micelles constitute self-assembling aggregates of the amphiphilic molecules. Hydrophobic regions of such molecules aggregate and form the core in the presence of water, while the hydrophilic parts remain at the outer surface. Micelles are very efficient at enhancing the solubility of hydrophobic drugs; however, they can also effectively encapsulate hydrophilic drugs, such as proteins and peptides. Because of their amphiphilic nature, micelles can penetrate the intestinal membrane and enhance the absorption of the drug into the bloodstream. In addition, micelles can enhance the stability and bioavailability of protein and peptide drugs by protecting them from hydrolytic and enzymatic degradation [25].

SLNs consist of solid lipids and are designed as controlled-release systems. The SLNs have a solid core at the temperature of the human body; they do not have the liquid lipid core as liposomes do, thus ensuring greater stability and prolonged release of the drug contained in them. Such slow release might be useful for prolonging the therapeutic action of the protein or peptide drug and minimizing peak-to-trough fluctuations in drug concentrations. SLNs are highly useful for proteins that need a long exposure to provide their therapeutic action, which is appropriate for chronic diseases like diabetes [26].

These lipid-based systems possess several important advantages, including improved drug stability, increased solubility, and better intestinal absorption-all of which are needed to maximize oral drug delivery for proteins and peptides.

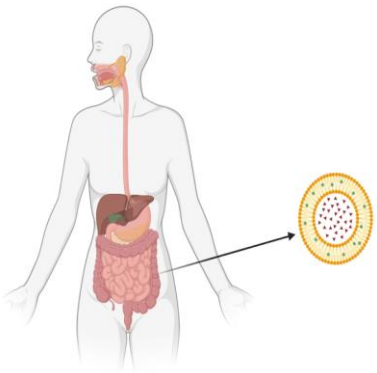

Figure 2. The proteins and peptides are encapsulated in a liposome and that liposome disintegrates in the GIT, which gives the therapeutic reaction. [63]

4.3 Polymer-based Drug Delivery Systems

Over the last few years, there has been tremendous interest in polymer-based drug delivery systems due to their wide applications and capabilities to improve oral bioavailability in proteins and peptides. Such systems consist mainly of biodegradable and biocompatible polymers, capable of encapsulating, stabilizing, and delivering protein-based drugs. Common polymers for such drug delivery systems include chitosan, PEG, PLGA, and PLA.

Polymeric nanoparticles represent one of the most studied polymer-based systems for drug delivery into proteins. These nanoparticles may encapsulate proteins and peptides in a form that shields them from enzymatic degradation in the GI tract. The polymer matrix can be engineered to release the drug at a controlled rate, thus improving drug retention at the site of absorption and enhancing bioavailability. These nanoparticles can be further functionally modified through conjugation to specific ligands or targeting moieties to ensure greater uptake through specific cells or tissues for improved targeted delivery [27].

Another promising avenue is the use of polymeric micelles from amphiphilic block copolymers for the delivery of proteins and peptides. The polymeric micelles may encapsulate hydrophilic as well as hydrophobic drugs and hence can enhance the solubility in the gastrointestinal tract. In addition, the polymeric micelles have been found to enhance the permeability of proteins and peptides through the tight junction’s disruption of intestinal epithelial cells for effective absorption [28].

Another type of polymer-based system that can be used to enhance oral delivery is hydrogels. Hydrogels are three-dimensional networks of hydrophilic polymers that can swell in the presence of water and form a gel-like structure which can encapsulate proteins

and peptides. Hydrogels are especially useful for sustained-release formulations since they can allow the release of the encapsulated drug over a period of time. This release profile is helpful in the retention of therapeutic concentration levels of protein drugs for an extended duration at the cost of a decreased frequency of dosing [29].

The polymer-based delivery systems, not only increase the stability and solubility of proteins and peptides but also deliver them in a targeted and controlled manner that is critical to maximize the therapeutic effect of such drugs.

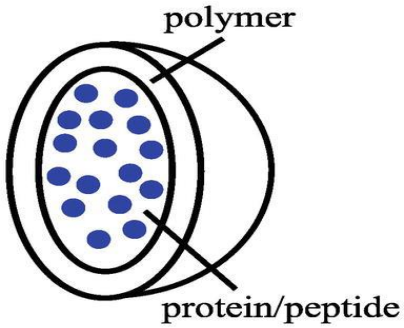

Figure 3. The proteins and peptides are encapsulated in a polymer which disintegrates, and gives the therapeutic reaction. [63]

5. Strategies to Enhance Stability and Bioavailability

Oral delivery of protein and peptide therapeutics has been one of the significant challenges in the pharmaceutical industry, majorly due to stability issues, enzymatic degradation, and poor permeability across the GI tract. From Figure 5, we can notice that, many strategies have been developed and refined with the aim of improving the stability, solubility, and absorption of such biopharmaceuticals. Generally, coating and encapsulation technologies, use of protease inhibitors and enzyme inhibition, and chemical modifications for absorption are applied to improve the oral bioavailability of proteins and peptides. In addition to preventing enzymatic degradation of the therapeutic proteins, these approaches enhance the transit of proteins and peptides across the GI membrane into systemic circulation.

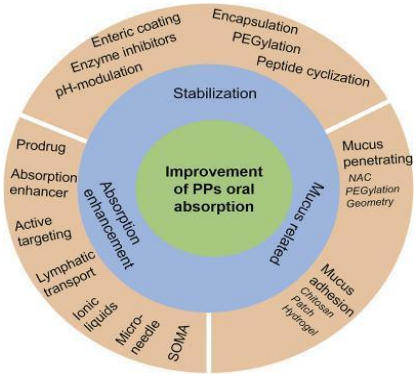

Figure 4. Flow chart of the general considerations in enhancement of oral bioavailability of PPs. [64]

5.1 Coating and Encapsulation Technologies

Among the most efficient techniques for enhancing protein and peptide stability and bioavailability are coating and encapsulation technologies. These strategies will mask the active pharmaceutical ingredient from the aggressive environment of the stomach and avoid proteolytic degradation to allow a higher portion of the drug to reach its site of action in the small intestine or blood circulation.

5.1.1 Polymeric coatings

Polymeric coatings are among the most frequently used drug administration technologies for orally giving protein-based drugs. Normally, these comprise biodegradable and biocompatible materials like chitosan, poly[lactic-co-glycolic acid] or PLGA, and polyvinyl alcohol. This polymer provides an additional physical barrier in the stomach for preventing the enzymatic degradation or

acidic degradation by gastric acid or digestive enzymes, respectively. Polymeric coatings can also be engineered to have a controlled release profile. For example, some drugs dissolve at particular pH values in the small intestine and are delivered where the absorption is most efficient [30]. This controlled release mechanism lets the active ingredient be released slowly and continuously, thereby enhancing the therapeutic effect of the drug while minimizing side effects.

Encapsulation in Liposome and Nanoparticle: This is another form of encapsulation for proteins and peptides, which offers much more protection against enzymatic degradation. Liposomes are lipid vesicles that can contain hydrophilic or hydrophobic drugs in their aqueous or lipid bilayer, respectively. Apart from providing protection against degradation, liposomes increase the solubility of proteins by creating a hydrophobic environment that makes them more soluble and absorbable in the gastrointestinal tract. Liposomes also improve the pharmacokinetics of proteins and peptides, which is the gradual release of the drug in the intestines, where absorption is most efficient [31]. Nanoparticles, usually composed of polymers, have similar benefits. Small size allows easy passage through biological barriers, and surface modifications improve their ability to target specific cells or tissues, thus improving drug delivery efficiency.

Coating and encapsulation technologies are significant improvements in stability, solubility, and controlled release for proteins and peptides, especially with polymers or liposomes. They are a promising option for oral delivery systems.

5.2 Protease Inhibitors and Enzyme Inhibition

Proteolytic enzymes within the gastrointestinal tract are among the major obstacles that face oral delivery of proteins and peptides. Since these proteolytic enzymes fragment large protein molecules into smaller peptides or amino acids, this is a serious issue that prevents these proteins from working. Therefore, the problem created by the existence of proteolytic enzymes led to the establishment of protease inhibitors and other enzyme inhibition approaches as a key component in enhancing the stability of protein and peptide drugs.

5.2.1 Protease Inhibitors

A protease inhibitor is a class of chemical or peptide reagent that selectively inhibit the activity of some digestive enzymes including pepsin, trypsin, and chymotrypsin, thereby stopping the breakdown of proteins and peptides in the stomach and small intestine. The two most frequently used protease inhibitors are soybean trypsin inhibitor and aprotinin, which, when combined with protein drugs, protect them against enzymatic cleavage [32]. The reduction in the activities of digestive enzymes ensures that larger fractions of intact proteins or peptides exist in a fully active conformation, consequently increasing their potency for therapeutic utility.

5.2.2 Enzymatic Degradation Reducing Strategies

Another strategy includes altering the pH environment or even co-administration of enzyme inhibitors that inhibit the action of proteolytic enzymes. For example, acid-neutralizing agents or PPIs might be used in the stomach for an increase in pH to inhibit proteases that perform well in such acidic conditions. Also, some inhibitors of enzymes function as competitive antagonists by competing with the protein and peptides at the active site of digestive enzymes. These strategies dramatically improve the bioavailability of protein-based therapeutics because more drug reaches its site of absorption in its intact form [33]. It is possible to protect protein and peptide drugs from premature degradation when they are administered orally through the use of protease inhibitors and techniques for enzyme inhibition. This makes them more bioavailable and stable.

5.3 Chemical modifications to improve absorption

Chemical modification of proteins and peptides: Another important method to increase bioavailability is to modify the chemistry of the proteins and peptides, which may offer better permeation across the GI epithelium and protect from enzymatic digestion.

5.4 Peptide modifications

In this approach, the peptide itself is modified with the aim to increase its stability against enzymatic cleavage. For example, including D-amino acids that are not susceptible to the action of proteolytic enzymes cleaving L-amino acids, or even just altering the backbone of the peptide, may provide the drug with increased resistance to proteolytic enzymes [34]. Other chemical modifications, like cyclization, which gives the ring structure higher stability, prevent peptides from enzymatic hydrolysis and improve their stability. Structural changes can also make peptides more hydrophobic, thus increasing their permeability across the lipid-rich membranes of the intestinal epithelial cells.

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5.5 Conjugation to Permeability Enhancers

Conjugation of proteins or peptides with permeability enhancers is another approach that can enhance absorption. Fatty acids, surfactants, or other amphiphilic molecules can be conjugated to peptides and proteins to increase their lipid solubility. These permeability enhancers allow the drug to more effectively traverse the intestinal membrane, which is typically impermeable to large, hydrophilic molecules [35]. This technique can be especially beneficial for proteins and peptides that are otherwise too large or hydrophilic to be absorbed efficiently.

5.6 PEGylation

A common chemical modification employed to improve the bioavailability of proteins and peptides is PEGylation, which involves attaching polyethylene glycol [PEG] molecules to the therapeutic protein. This modification increases the solubility of the protein, reduces its immunogenicity, and extends its half-life in blood circulation by protecting it from the immune system, which clears proteins very rapidly [36]. Besides enhancing the stability of proteins and peptides, PEGylation enhances the absorption of the drug since the interactions of the drug with proteolytic enzymes are diminished.

Chemical improvements on the absorption system are critical for the viability of protein and peptide drugs as a form of oral delivery. Improved stability, solubility, and permeability enhance the drugs' ability to be transported to systemic circulation in a more efficient manner where the therapeutic effects can be delivered.

5.7 Permeation Enhancers and Transport Mechanisms

From figure 3, we can observe that, the degree of oral bioavailability of protein and peptide drugs is determined by the capacity to cross the cellular barrier to enter the bloodstream. Various strategies have been explored throughout the years in order to enhance the absorption of these macromolecules. These strategies include: the use of absorption enhancers, transporter-mediated uptake mechanisms, and nanotechnology. Aim of these approaches is to enhance the passage of the drug across the intestinal epithelial layer and, therefore, to increase their absorption and bioavailability.

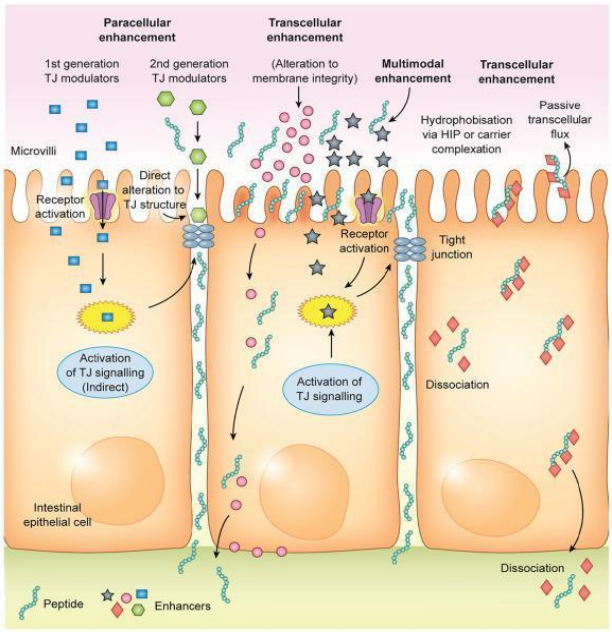

Figure 5. The schematic illustration of mechanisms of absorption enhancers including transcellular and paracellular pathways. [63]

6. Mechanism of Action of Absorption Enhancers [e.g., Surfactants, Bile Salts]

Absorption enhancers are used extensively in circumvention of permeability barriers of the gastrointestinal tract. It assists in enhancing the solubility of a drug, enhances the permeation of the drug across the intestinal epithelial barrier, and inhibits the enzymatic degradation of a drug. Two principal classes are surfactants and bile salts used in delivery of proteins and peptides.

6.1 Surfactants

Surfactants are amphiphilic molecules that alter the structure of the intestinal cell membranes to be more permeable for larger molecules such as proteins and peptides. Surfactants modify the membrane fluidity of the lipid bilayer, leading to an easier passage of the drug through them. Some of the surfactants which have been used for the enhancement of permeation include polysorbates, Tween 80, and cetyl-trimethyl-ammonium bromide [CTAB]. Such surfactants positively come in contact with intestinal epithelial cells, enhancing the solubility and absorption of poorly water-soluble drugs at the same time. However, optimization must be done for the use of surfactants to avoid their toxicity and irritation on contact with the gut lining at higher concentrations [37].

Bile Salts: Bile salts are endogenous compounds produced in the liver and secreted into the small intestine. They have been known for a long time to improve the absorption of both hydrophobic and hydrophilic drugs. Bile salts assist in the solubilisation of hydrophobic compounds and their transport across the intestinal wall. Bile salts can also emulsify lipids, forming micelles that transport hydrophobic drug molecules. These surfactant-like properties are beneficial for the oral delivery of protein and peptide therapeutics, as bile salts can help protect the drug from enzymatic degradation in the stomach and increase its solubility in the small intestine, where absorption is maximized [38].

One significant application of the surfactant and bile salts as absorption enhancers has emerged, which deals with the bettering of protein and peptide drug bioavailability. More optimization and studies are essential for the further development of safer and effective formulations using these absorption enhancers.

6.2 Transporter-Mediated Uptake [Peptide Transporters, ABC Transporters]

Transporter-mediated uptake is another mechanism that can significantly enhance the absorption of proteins and peptides across the intestinal epithelial cells. Transporters are specialized proteins located on the cell membrane, which facilitate the movement of drugs from the intestinal lumen into the bloodstream. There are two major classes of transporters that are particularly relevant for protein and peptide delivery: peptide transporters and ATP-binding cassette [ABC] transporters.

6.2.1 Peptide Transporters

The peptide transport system, the human peptide transporter 1 being one of the most important peptides, is important for the absorption of small peptides and some derivatives of proteins. PEPT1 is involved in the active transport of di- and tripeptides, formed from the action of digestive enzymes that cleave larger proteins into smaller units in the digestive tract. The PEPT1 transporter is of the proton-dependent type and is highly expressed in the small intestine; thus, this might be one of the major absorption pathways for peptide-based drugs [39]. This transporter can be exploited to make drugs absorbable as intact peptides instead of being digested by enzymes in the gastrointestinal tract.

6.2.2 ABC Transporters

ABC transporters include P-glycoprotein [P-gp] and multidrug resistance proteins [MRPs]. These transporters are known to efflux various drugs from cells, including intestinal epithelial cells. Although these transporters are generally involved in preventing the absorption of xenobiotics and drugs, they also play a critical role in the disposition and bioavailability of protein and peptide drugs. Inhibition of these transporters significantly increases the bioavailability of proteins and peptides, as it prevents their active efflux back into the gastrointestinal lumen [40]. Understanding this role of ABC transporters in drug absorption is important for developing strategies to improve the bioavailability of orally administered protein-based drugs.

Transporter-mediated uptake, especially via PEPT1, and the regulation of ABC transporters are promising strategies for enhancing the absorption of proteins and peptides by enhancing their transport into the bloodstream.

6.3 Enhanced Permeation Viability based on Nanotechnology

Nanotechnology strategies are recently among the most innovative and efficient in enhancing permeability of protein and peptide drugs across biological membranes. Nanoparticles, nanoscale liposomes, and other nanomaterials consequently permit a variety of advantages for drug delivery, such as increased surface area, controlled drug release, juxtaposition for enhanced targeting abilities, etc.

6.3.1 Nanoparticles

Among nanoparticles, some were studied for the improvement of oral delivery of proteins and peptides. These include nanoparticles composed of biocompatible materials such as PLGA and chitosan. Such particles may be encapsulated within proteins and peptides to protect them from degradation by enzymes, and for further transport across the intestinal epithelium through endocytosis. Due to the very small size of nanoparticles, they can also help penetrate through the mucus layer and tight junctions between the epithelial cells more effectively, thus improving drug absorption [41]. More importantly, regulation of the drug release from nanoparticles provides a greater stability for many drugs and enhances the bioavailability for extended therapeutic activity.

6.3.2 Nanoscale Carriers

Liposomes and micelles: Liposomes and micelles are nanoscale drug carriers prepared from lipids and capable of encapsulating both hydrophobic and hydrophilic drug molecules. More importantly, these systems have been documented to enhance solubility and stability of proteins and peptides, thereby improving their absorption from intestinal epithelial cells. Liposomes, being lipid-based, have a higher affinity for the cell membranes of intestinal cells, thus contributing to enhancement of drug delivery across the lipid bilayer. Micelles are amphiphilic nanoparticles able to solubilize hydrophobic drugs; through their capacity to solubilize hydrophobic drugs, micelles increase the permeability of drugs in an aqueous environment of the gastrointestinal tract. Liposomes and micelles can also be further modified with targeting ligands in order to enhance the specificity toward particular intestinal cell receptors and thereby increase the absorption of drugs [42].

6.3.3 Nano-emulsions

The third nanotechnology-based approach is comprised of nano-emulsions, which can be defined as colloidal systems consisting of an oil phase and a water phase stabilized by surfactants. These emulsions are able to solubilize poorly water-soluble peptides and proteins for better oral bioavailability. The nanoscale size of the droplets in the nano-emulsion allows better interaction with intestinal cells, enhancing the permeation of the encapsulated drug. Nano-emulsions have been reported to be very effective in enhancing the absorption of hydrophobic drugs, and when used along with proteins or peptides, it enhances the bioavailability of the therapeutic as a whole [42].

Nanotechnology-based approaches are one of the most novel strategies to achieve oral bioavailability of protein and peptide drugs. The design of nanoparticles and nanoscale carriers that protect, solubilize, and deliver drugs specifically to cells makes nanotechnology extremely valuable for developing more effective and efficient oral protein and peptide therapeutics.

7. Oral Delivery of Peptides: Formulation and Development

The main challenges for the oral delivery of peptide therapeutics arise from their intrinsic instability and susceptibility to enzymatic degradation within the gastrointestinal tract. Effective formulation development is thus essential to stabilize these molecules, prevent aggregation, and enhance their bioavailability.

7.1 Peptide Aggregation and Formulation Strategies

Peptide aggregation can compromise both therapeutic efficacy and safety. Determinants of aggregation include peptide concentration, temperature, pH, and interactions with formulation excipients. A number of strategies are used to minimize aggregation.

Incorporation of Surfactants: It has been customary to include surfactants such as polysorbates 80 into formulations that will stabilize the peptide, ensuring prevention of aggregation at the stage of manufacturing and during storage. However, these surfactants must be chemically stable because their breakdown reduces the stability of peptides [49].

Including Stabilizers: Some excipients, like sugars and polyols, stabilize peptides by maintaining their native form and preventing aggregation. It is essential to choose stabilizers that are specific to a particular peptide and breakdown process [50].

Benefits of solid dose forms include patient compliance, stability, and simplicity of handling. However, significant thought must be given to the formation of peptides into solid forms.

Encapsulation of peptides in tablets or capsules necessitates the use of excipients, which are without causing degradation and aggregation when such encapsulation takes place directly. There can be application of protective coating so that protection to the

acidic environment of stomach takes place by coating for an eventual release within the intestine when it becomes slightly neutral [51].

7.2 Powder Formulations

Peptide powders can be reconstituted before injection or filled into capsules. Lyophilisation, or freeze drying, is the most commonly used method for converting peptide solutions to powders that are stable and free of aggregation [52].

7.3 Fluid Compositions and Their Benefits

Although liquid peptide formulations are easier to administer, they are quickly absorbed, and it is challenging to keep peptides stable in aqueous solutions.

7.4 Stabilization Techniques

To improve the stability of peptides in liquid formulations, stabilizers are added and pH is changed. For instance, aggregation can be reduced by keeping the pH around the peptide's isoelectric point. Additionally, during administration and storage, surfactants may inhibit surface-induced aggregation [53].

SMEDDS, or self-micro-emulsifying drug delivery systems, are an isotropic blend of oils, solvents, and surfactants that spontaneously create micro-emulsions when they come into contact with gastrointestinal fluids. They improve the solubility and bioavailability of hydrophobic peptides and shield them from enzymatic degradation. SMEDDS can be prepared as liquids or be incorporated in solid dosage forms, which gives room for a lot of variability in peptide delivery [54].

8. Gastrointestinal Tract Targeting and Controlled Release

Targeting precise sites within the GI tract along with controlled release of drugs at these sites could significantly improve therapy and reduce toxicity. Some of these objectives have been addressed through developing pH-sensitive or time-dependent delivery systems.

8.1 Targeting Specific Sites in the GI Tract

The GI tract has different conditions, such as pH, enzymes, and residence times, at different locations along its length; these can be exploited to design drug delivery targeting specific regions within the GI tract:

8.1.1 Stomach: Formulations may be designed to float in order to ensure longer gastric residence times. Coatings that are pH sensitive and dissolve in the acidic stomach environment can be used to enhance site-specific drug delivery [55].

8.1.2 Small Intestine: Enteric coatings are commonly employed to prevent drug release in the stomach's acidic environment, allowing dissolution and absorption in the more neutral pH of the small intestine. This approach protects acid-labile drugs and reduces gastric irritation [55].

8.1.3 Colon: Colon specific drug delivery systems [CDDS] are welcome for the site-specific treatment of local diseases like ulcerative colitis. The most common strategies use pH-sensitive polymers that disintegrate or dissolve at higher pH of colon or time dependent systems that exhibit a lag release of the drug after a predetermine lag period [55,56].

8.2. Controlled release mechanisms for extended drug delivery:

Controlled Release Systems are fabricated to maintain continuous plasma drug levels for long term periods, making the therapy response better and increase patient compliance.

8.3 Matrix Systems: Drugs are dispersed in a polymer matrix that controls the release rate through diffusion or degradation mechanisms. The release kinetics is determined by the choice of polymer and its properties [57].

8.4 Reservoir Systems: These are systems consisting of a core that contains the drug, surrounded by a rate-controlling membrane. The drug diffuses through the membrane at a controlled rate, which allows for sustained release [56].

8.5 Osmotic Systems: The osmotic pressure-based systems release drugs at a controlled rate that is independent of the external conditions. These systems consist of a semi-permeable membrane and an osmotic core that ensures uniform drug release [57].

8.6 pH-Sensitive and Time-Dependent Release Systems

PH-sensitive and time-dependent systems are highly effective for targeting specific regions of the GI tract:

8.6.1 pH-Sensitive Systems: The systems use pH-sensitive polymers that respond to the pH gradient along the GI tract. For example, some of the polymers are stable at the acidic stomach pH but degrade when the pH in the intestine increases, allowing for specific drug delivery [56].

8.6.2 Time-Dependent Systems: These are also called pulsatile release systems, and they are intended to deliver the drug after a certain lag time, which corresponds to the transit time to the target site. This approach is useful for drugs that need to be released at a certain time or location in the GI tract [57, 58].

Table 1: Oral peptide and protein delivery systems that are either in clinical trials or commercialized. [62]

Approach	Peptide/Protein	Dosage form
Permeation enhancer	Insulin Insulin	Enteric-coated capsule Capsule
	Leuprolide	Tablet
	Parathyroid hormone [PTH] Salmon calcitonin	Tablet Tablet
	Salmon calcitonin	Enteric-coated capsule
	Salmon calcitonin	Tablet
	Semaglutide	Tablet
Lipid-based formulation	Cyclosporine Exetanide	Capsule Solution Capsule
	Insulin	Gel capsules
	Insulin	Enteric-coated tablet
	Insulin	Solution [Buccal spray]
	Octreotide	Capsule
Chemical modification	Dolcanatide	Tablet
	Desmopressin	Tablet
	Insulin	Tablet
	Linaclotide	Capsule
Nanoparticles with hydrophobic surface	Insulin	Capsule
pH sensitive formulation	Plecanatide	Tablet

9. Future Directions and Challenges in Oral Delivery of Protein and Peptide Drugs

The oral delivery of protein and peptide drugs is a challenge due to their inherent instability and poor absorption in the gastrointestinal tract. Advances in personalized medicine, overcoming resistance to oral protein delivery, and the emergence of novel technologies like mRNA therapeutics are paving the way for future developments in this field.

9.1 Personalized Medicine and Patient-Specific Formulations

Personalized medicine tailors therapeutic interventions to individual patient characteristics, enhancing efficacy and minimizing adverse effects. In the context of oral protein and peptide delivery, this approach involves customizing formulations based on a patient's genetic profile, disease state, and gastrointestinal physiology. Such customization can improve drug absorption and therapeutic outcomes. For instance, advancements in peptide drug discovery and modification have enabled the development of therapies that are more specific to individual patient needs [58].

9.2 Future Technologies: mRNA and Beyond

There is significant interest in mRNA therapeutics, particularly in the wake of the success of mRNA-based vaccines. mRNA therapies open up the possibility of the in vivo production of therapeutic proteins without the need for direct oral protein delivery, overcoming the problems related to it. It is possible that cells, with mRNA encoding a protein, will be able to synthesize the therapeutic agent intracellularly, properly folded and with appropriate post-translational modifications. The technology also lends itself to rapid development and scalability [59].

The new field of non-coding RNA [ncRNA] therapies, including antisense oligonucleotides and small interfering RNAs [siRNAs], has opened up a new horizon in the modulation of gene expression and treatment of many diseases. These therapies can be designed to target specific mRNA sequences for the degradation of disease-causing proteins or the upregulation of therapeutic ones [60, 61].

10. Conclusion: The Future of Oral Peptide and Protein Therapeutics

10.1 Summary of Current State and Advances

Poor absorption in the gastrointestinal system and enzymatic degradation have posed challenges to oral administration of peptide and protein therapies. However, sophisticated drug formulations, which were comprised of enteric coatings, nano-carriers, and permeation enhancers, improved bioavailability and stability. PEGylation and other chemical changes, together with personalized medicine, further improved treatment results. Protein treatments now have more options thanks to the development of mRNA-based vaccinations.

10.2 Future of oral protein & peptide drug delivery

Even though there has been improvement, there are still a number of obstacles to overcome, particularly in hostile GI tract conditions. Future solutions will come from more recent technology like enzymatic inhibitors, complex nano-carriers, and their combinations. The development of personalized medicine treatments based on each patient's unique profile will continue, and RNA-based therapy presents an exciting substitute for oral medication administration. Smart polymers, nanoparticles, and probiotics may further enhance absorption and stability in the future.

The future of oral peptide and protein therapeutics is very promising, but ongoing research and collaboration are needed to overcome current limitations and unlock new treatment possibilities.

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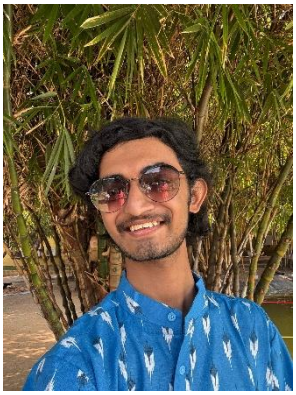	Commi Lalith Avneesh Student B.V, Raju Institute of Technology, Narsapur, Medak, Telangana - 502313

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