

Pharmaceutical Advancements in the Oral Administration of Biologics

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Patients tend to prefer the oral administration of medication, as it is typically the easiest and most convenient [1]. It is typically the most advantageous route for physicians due to its many benefits including non-invasiveness, patient compliance, and convenience of drug administration [2]. Despite this, the oral administration of biologics has yet to be proven effective due to the physiological barriers of the gastrointestinal tract. The gastrointestinal tract presents multiple barriers that limit the systemic absorption of complex macromolecules after ingestion. Various factors govern oral drug absorption including drug solubility, mucosal permeability, and stability in the gastrointestinal tract environment. Biologics are highly sensitive to the harsh environment of the GI tract. In addition to this issue, the relatively large molecular size of biologics causes the permeability across the intestinal mucosa to become extremely poor.

Research in the field of drug discovery and design has proliferated the ways in which we administer medications in a clinical setting and the growth of biologics in recent decades has further accelerated research activity. Different pharmaceutical technologies and drug delivery systems including nano carriers, micelles, cyclodextrins, and lipid-based carriers have been explored to enhance oral drug absorption. This article will serve to address the main physiological barriers to oral delivery of biologics and discuss different research strategies to improve the effectiveness of oral delivery. Additionally, this discussion will highlight the advantages and limitations of oral drug delivery systems as well as the overall viability and potential of this future clinical field.

Keywords

Oral delivery, Drug discovery, Biologics.

Introduction**The Role of Biologics**

Biologics are medicines that influence various products from living organisms such as recombinant proteins and vaccines. Biologics have ultimately revolutionized and improved the management of various conditions such as inflammatory diseases, cancer, and diabetes. Although biologics have been used in clinical settings for decades as in the case of insulin, the development of administering biologics has increased significantly. Due to advancements in biotechnology and a wider understanding of biological diseases,

the overall development and efficiency of biologics have improved.

Biologics differ from chemically derived pharmaceuticals and other conventional medicines in a variety of ways, primarily with implications surrounding the administration, production, associated costs, and clinical efficacy [3]. Biologics generally have higher molecular weight and an inherent heterogeneous structure that differs from small molecule drugs. Due to the size and complexity of biologics, they are increasingly sensitive to the physical and chemical conditions of the gastrointestinal tract. Because of this sensitivity to the internal environment, the vast majority of biologics are currently administered through injection rather than oral ingestion.

Advantages of Oral Delivery Systems

One component of the patient treatment experience is the way in which therapy is administered. The compliance of patients to oral formulations is generally higher than that of other parenteral routes such as intravenous, subcutaneous, and intramuscular injections, as well as inhalation for asthma medications. Ingestion as opposed to injection also can offer additional benefits in the form of physiological mimicry. For instance, oral consumption of insulin can mimic the physiology closer to the physiology of endogenous insulin secreted by the pancreas. Furthermore, oral consumption can minimize any needle-related complications and costs associated with administration. Orally administered drugs can be targeted to particular regions within the gastrointestinal (GI) tract for localized treatment of pathological conditions such as stomach and colorectal cancers, infections, and inflammations.

Drugs administered orally (e.g., tablets, capsules, syrup, solutions, suspensions, powders, emulsions, etc.) are placed in the mouth and swallowed. Oral drug delivery provides an effective option for treating various fatal diseases because of its several benefits such as ease of administration, patient compliance, and cost-effectiveness. Current estimates indicate that oral formulations represent about 90% of the global market share of all pharmaceutical formulations intended for human use. Around 84% of the best-selling pharmaceutical products are orally administered and are currently valued at \$35 billion [1]. Typically, orally administered drugs are the most convenient for repeated and prolonged use. Patients can self-administer treatments in non-sterile conditions, which can be an added benefit for patient compliance.

Advancements in the Field of Oral Biologics

Despite ongoing research in the oral delivery of biologics, the current reality of clinical application has remained stagnant regarding the therapeutic administration of biologic medications. However, the spread of biologics on the pharmaceutical market has intensified the research activity on the possibility of clinical application. In combination with advances in technology, research into oral delivery of biologics is increasingly producing more clinically relevant drug-delivery technologies, with the potential to make oral administration of biologics a viable option. Some viable design options such as the prodrug design can improve the oral bioavailability of drugs by enhancing their water solubility and gastrointestinal permeability and overcoming first-pass metabolism. Design models of pharmacokinetic principles can be utilized to further the research of biologics in a clinical setting.

Uptake of Biologics

Physiological Barriers to the Oral Uptake of Biologics

One of the largest challenges in achieving clinical oral delivery of biologics is to overcome the physiological barriers of the GI tract. The GI tract is responsible for preventing the uptake of foreign materials, including harmful pathogens or their products, from the external environment. Another barrier to the uptake of biologics is the chemical barrier found within the gastrointestinal environment. A major chemical barrier is the pH-induced proteolysis of proteins into constituent amino acids, dipeptides, and tripeptides. The

largest and most important barrier to the absorption of biologics is the intestinal epithelium. Although it is a single cell thick, its cells are arranged to form a near-continuous cell membrane barrier facing the lumen. Furthermore, the mucus layer of varying thickness (depending on the region of the gut) that sits above the epithelium may also act as a barrier, hindering the diffusion of biologics to the underlying epithelium [4]. Basement membranes, which are located between the epithelial and connective tissue as thin and specialized sheets of extracellular matrix, can hamper the penetration of macromolecules into the space beneath the epithelium, thus limiting systemic absorption. These factors significantly contribute to biopharmaceuticals having oral bioavailability of less than 1%. In addition, the absorption of drugs can be limited by their poor chemical and biological stability, as well as by physiological barriers, including pH, efflux transporters, and metabolic enzymes.

Biological barriers within human anatomy affect the absorption rate of orally administered biologics. Most orally administered medications are primarily absorbed by the duodenum and jejunum in the upper parts of the GI tract. The drug absorption ability of the stomach is less than that of the intestine because of the smaller surface area and a thicker mucus layer. The epithelial lining of the intestines is one of the major barriers to drug absorption in the GI tract. Epithelial cells are arranged in a single-column layer that is mainly accountable for the passage of hydrophilic molecules. About 3,000–7,000 microvilli per cell in the small intestine provide a large surface area for drug interaction and absorption; however, they additionally provide an enzymatic barrier since the brush border is concentrated with digestive enzymes [5]. Overall, absorption of drugs from the lumen of the GI tract requires their passage through multiple layers including gastric juice, pericellular matrix, and mucous-rich layer, to reach the epithelium, mucosa, and blood or lymph capillary walls. These biological barriers can propose a problem when orally administering biologics due to the sensitive nature of these drugs.

Another factor that influences drug absorption is the pH of the GI fluid thus, drugs with poor stability under acidic pH need to be protected in the stomach. The active movement and contraction of the GI tract can also affect the bioavailability of orally administered biologics. The peristalsis motilities primarily determine the passage rate and thus, the residence time of a drug after oral administration. As drugs travel throughout the GI tract, they have the potential to cross the mucous membranes of the GI organs including the mouth, esophagus, stomach, duodenum, jejunum, ileum, and colon. If they are not able to cross the membranes by the time they reach the colon, they end up eliminated in the feces and will not be completely absorbed by the intestine.

Food can also influence the absorption of drugs: it can decrease, increase, delay, or accelerate drug absorption. Food affects the GI functions such as gastric emptying, intestinal transit time, bile acid secretion, stomach pH change, and liver blood flow increase. Further, it can alter the physicochemical characteristics of drugs, such as solubility, intestinal permeability, size, and dissolution

profile. In general, hydrophobic drugs or drugs with solubility that are pH-dependent can be influenced by the food consumed during the time of administration. In addition to solubility and permeability, drug metabolism can also influence their oral bioavailability.

Methods for Improving Oral Delivery of Biologics: Reduction of Acid and Enzyme Degradation

One strategy that can enhance the bioavailability of biological medicines is reducing acid degradation. This can be achieved through the delivery of medication with an enteric coating or a polymer barrier applied to oral medication that prevents its dissolution or disintegration in the gastric environment. It is also possible to modify the chemical structures of some biologics, particularly peptides, in order to improve their stability in the GI fluids. Some biologics have higher intrinsic physicochemical stability against enzymatic degradation in the GIT and may show potential for oral delivery [6]. Protection of the biological drug from acid and enzymatic degradation is an important requirement and any strategies that seek to improve oral delivery of biologics.

Prolonging the gastric residence time of dosage forms is particularly beneficial for drugs that are predominantly absorbed in the stomach or upper GI tract, or for drugs that suffer from solubility issues in the intestinal fluid. This promotes the slow release of drugs in the stomach, which subsequently extends the time available for drug dissolution and absorption in the stomach and/or small intestine [7]. The benefit of this approach also includes sustained or controlled release drug delivery, which can reduce fluctuations in systemic drug concentrations as well as increase patient compliance to medications by minimizing the number of doses required. The ability to successfully predict the pharmacokinetic properties plays a crucial role in the selection of candidate drugs and significantly reduces the number of potential failures in drug development.

Methods for Improving Oral Delivery of Biologics: Increase Viability and Longevity of Absorption into the Epithelium

The purpose of this method is to prevent the luminal loss of the medicine, which is important considering the length of the intestines. ‘Mucoadhesive’ materials are typically polymers capable of interacting with the mucus membrane of the GI tract. These mucoadhesives can help prolong the medicine’s residence time at the absorption site, leading to enhanced absorption [8]. While mucoadhesive systems have demonstrated potential for enabling oral delivery of biologics in vitro and in vivo, potential challenges facing this strategy include limited efficacy, particularly with larger biologics. Simply prolonging the residence time of the biotherapeutic at the absorptive surface may not be sufficient to achieve clinically relevant improvement of bioavailability. Mucoadhesive dosage forms may be designed to enable prolonged retention at the site of application, providing a controlled rate of drug release for improved therapeutic outcomes [7]. Application of dosage forms to mucosal surfaces may be of benefit to drug molecules not amenable to the oral route, such as those that

undergo acid degradation or extensive first-pass metabolism. The mucoadhesive ability of a dosage form is dependent upon a variety of factors, including the nature of the mucosal tissue [9].

To overcome deficiencies of absorption due to drug properties, the dosage form may help improve absorption by altering the disintegration and dissolution time, increasing residence time in the intestine, and providing delayed release in the lower intestine instead of the stomach. The absorption of the drug through the GI tract is governed by either a simple passive diffusion or active transport with the aid of transporters located in the GI tract. For most drugs, passive diffusion is the mode of transport. The amount of drug absorbed is dictated by the gradient created across the membranes in the stomach and the small intestine as well as the chemical structure of the drug molecule itself such as the size and degree of ionization.

Methods for Improving Oral Delivery of Biologics: Increase the Permeability of the Mucosal Membrane

The most commonly researched strategy for improving the oral bioavailability of biologics is to increase the permeability of the mucosal membrane as both the intestinal mucus barrier and the epithelial barrier can be modified. Modifying the mucus barrier by using mucolytic (mucus-breaking) agents can improve the diffusion of large molecule biologics. The epithelial barrier can be modified via several chemical absorption enhancers, including surfactants and other materials that open epithelial tight junctions.

Surfactants are substances that tend to reduce the surface tension of a liquid in which it is dissolved. These contain both hydrophilic and hydrophobic components thereby facilitating the permeation of macromolecules. Surfactants have several uses in pharmaceuticals, for solubilization of hydrophobic drugs in aqueous media, as components of emulsions, surfactant self-assembly vehicles for oral and transdermal drug delivery, as plasticizers in semisolid delivery systems, and as agents to improve drug absorption [10].

Another modification that can be made to the epithelial barrier is the tight junction opening permeation enhancer. Epithelial tight junction opening is a potentially useful approach to increase the permeability of the intestinal epithelium as the medicine can avoid entering the epithelial cells and be present in an enzyme-rich cytoplasmic environment during its absorption process [11]. The process involves widening the space between adjacent epithelial cells, which is normally too small to accommodate biologics. Drug delivery approaches that employ chemicals to modify the mucosal barrier — namely absorption enhancers, such as surfactants and tight junction-opening agents — rely on concentration-dependent effects on barrier permeability. Therefore, clinical implications of this method may relate to potential variability in absorption because of fasted and fed state, as well as the volume of water used for swallowing solid dosage forms. In addition, the long-term effects of repeated alteration of GI permeability currently remain unclear and require careful evaluation.

Methods for Improving Oral Delivery of Biologics: Increase the Permeability of the Biologic Drug

Another method to improve the oral bioavailability of biologics is via a chemical modification to alter the molecule to impart its epithelial-permeating properties. It is also possible to increase the ability of the biotherapeutic to cross the intestinal epithelium by attaching it to another molecule that is capable of doing so. The “transport-enabling molecule” can be attached through chemical attachment or via biotechnology-mediated fusion technologies [12]. Examples of transport-enabling molecules include other peptides or proteins that utilize biological transport processes to traffic across the epithelium. Biologic carriers can be based on biodegradable polymeric nanoparticles, which have numerous advantages. For example, some nanoparticles offer protection of the therapeutic drug from acid and enzymes present in the GI tract. Selective drug delivery can be achieved by targeting specific receptors located on the surface of intestinal epithelial cells. However, similar to large molecule biologics, nanoparticle carriers are typically poorly absorbed across the intestinal mucosa [13].

Nanoparticle-based drug carriers for the oral delivery of biologics are engineered with specific materials on their surface that act as ligands for biological transport receptors. Several research groups have explored such delivery systems, including nanoparticles exploiting the intestinal epithelial transport pathways of immunoglobulin G and vitamin B12. These systems moved across the intestinal epithelium faster and largely when compared with unmodified nanoparticles [14].

Permeability across biological membranes is a key factor in the absorption and distribution of drugs. Poor permeability can arise due to a number of structural features, as well as membrane-based efflux mechanisms. [15] Membrane permeability tends to restrict the transfer and distribution of drugs once they are delivered to the tissue. While these compounds are pharmacologically effective, poor absorption due to low permeability becomes the rate-limiting step in achieving adequate bioavailability. Several approaches have been explored and utilized for improving the permeability profiles of these compounds.

Methods for Improving Oral Delivery of Biologics: Ingestible Emerging Technologies to “Bypass” The Mucosal Barrier

In addition to being capable of protecting the therapeutic from the hostile environment of the GIT, ingestible ‘smart’ devices can be used to enhance the intestinal absorption of biologics through different means, including ultrasound and microneedles [16]. The microneedle technology involves a capsule designed to remain intact in the stomach and once in the small intestine, it injects the medicine into the intestinal wall. This is a painless process due to the absence of pain receptors in the intestinal mucosa and has shown impressive insulin bioavailability that is equivalent to or better than subcutaneous injections. The advantage of this technology is that as well as the delivery of low-to-medium molecular weight biologics, it may also be able to deliver larger biologics, such as antibodies.

Capsules encasing the microneedles can be coated using a pH-responsive material to reduce degradation. Using transmitter and receptor cells, the coating can dissolve and release the microneedles. In the case of systems with hollow microneedles, the drug reservoir is compressed through peristalsis, releasing the drug through the needles. For systems with solid microneedles, the drug is formulated into the microneedles that penetrate the tissue and break off from the pill, leaving the needle to release the drug in a controlled manner based on the needle formulation. After drug release, the microneedles remain lodged in the GI tissue until biodegradation.

Another recent technological advancement termed the ‘self-orienting millimeter-scale applicator’ (SOMA), can manipulate the physical design of the medication to administer a biologic via a biodegradable microneedle [17]. This system for the oral delivery of biologics uses this same shape and low center of gravity to self-orientate in a correct position and physically insert a biodegradable microneedle through the stomach mucosa for systemic administration of biotherapeutics.

Conclusions

Devices for oral delivery systems of biologics are showing significant potential and progress geared toward medical advancement; however, research within this field is still scarce. While all of the discussed drug delivery strategies have shown significant results in possible pharmacokinetic scenarios, they have yet to be clinically proven effective by patients. Unfortunately, with many of the delivery approaches discussed above, safety and efficacy are often mutually exclusive and, therefore, such strategies are unlikely to progress to the clinic. Furthermore, it is well known that many of the permeation enhancers in current oral peptide clinical trials cause small intestinal epithelial damage. Although tissue damage can be reversible and is often temporary, research has yet to prove if chronic tissue damage from such absorption enhancers could result from continued and prolonged use.

A safer alternative could be one that relies on improving the intestinal absorption of biologics by exploiting biological transport processes to achieve delivery without damaging the tissue; however, these are likely to be faced with limited capacity and may be best suited for biologics that are more potent. Furthermore, the costs of these technologies are currently unclear, but are likely to be high in the short-to-medium term — in which case, it will be critical to consider the selection of the biologic, disease area, and patient population for use of these drug delivery systems.

Research into oral delivery of biologics has made considerable progress, yet has not produced a significant impact in the clinic to date. The lack of clinical translation success in this area, which partly reflects the highly effective physiological barriers in the gastrointestinal tract, has usually been related to the safety of drug delivery approaches. However, increased knowledge of the physiological barriers, coupled with unprecedented recent developments in materials, are propelling advances in this area, and are likely to make oral delivery of biologics a clinical reality.

Future Trends

Oral drug delivery is one of the most common routes of drug administration in both adult and pediatric patients. Conventional oral formulations can raise issues and complications that could be addressed by advanced formulation strategies. One critical aspect that still deserves more consideration in the future is the establishment of reliable in vitro-in vivo correlation models to predict better in vivo performance and to generate data that offer cost-benefit over existing formulations [13]. This will help accelerate the transition of more realistic and more relevant formulations from laboratory to commercial production scale. Additionally, the target population of patients must be taken into account when designing new formulations. Future research can be directed toward the development of better pediatric formulations by using nanoparticle technologies that are currently used for developing drug formulations for adults.

It is expected that the overall time for formulation development will be shorter than the currently existing one to bring a lead compound from drug discovery to clinical trials. However, there are numerous obstacles that pharmaceutical researchers will have to face to accomplish better and more effective oral formulations that can provide better therapy.

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