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AN OVERVIEW OF RECENT DEVELOPMENTS IN THE ORAL DELIVERY OF BIOLOGICS

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ABSTRACT :

Biologics have long been difficult to give orally due to enzymatic breakdown, poor absorption, and low bioavailability in the gastrointestinal tract. However, recent improvements in drug formulation and delivery technology have showed considerable promise in breaking down these barriers, potentially altering the way biologic medicines are administered. Key advancements include the creation of nanocarriers such as liposomes, micelles, and nanoparticles, which shield biologics from degradation and improve absorption. Furthermore, the application of permeability enhancers, enzyme inhibitors, and pH-sensitive polymers increased the stability and absorption of biologics in the hostile environment of the digestive system. Recent initiatives have concentrated on developing targeted delivery systems capable of releasing biologics in specific areas of the gastrointestinal tract, which enhances therapeutic effectiveness while reducing side effects. The incorporation of intelligent drug delivery technologies, such as responsive carriers that activate drug release in response to particular conditions, further improves the prospects for oral biologics. However, there are still numerous challenges to overcome, including issues related to scalability, regulatory requirements, and cost-effectiveness. Additionally, ensuring the safety and stability of biologics as they pass through the digestive system remains a significant challenge. Nonetheless, progress in oral delivery systems for biologics presents considerable potential.

KEYWORDS : Oral biologics, nanoparticle, liposomes, hydrogels,mucoadhesive polymers,enzyme inhibitors

INTRODUCTION

The oral administration of biologics has become a key focus in pharmaceutical research, driven by the growing need for patient-friendly alternatives to traditional injection methods. Biologics, which encompass peptides, proteins, monoclonal antibodies, and vaccines, have demonstrated significant effectiveness in managing chronic and complex conditions such as diabetes, cancer, and autoimmune diseases[1].Nevertheless, delivering these biologics orally presents considerable challenges due to their large molecular size, intricate structures, and vulnerability to enzymatic breakdown in the gastrointestinal (GI) tract. Furthermore, the limited permeability of the intestinal epithelium and their instability in acidic conditions greatly restrict the bioavailability of biologics taken orally.Recent progress in drug delivery technologies is helping to address these challenges[3]. New and innovative approaches, including nanoparticle and microparticle carriers, liposomes, and hydrogels, are being developed to enhance the oral delivery of biologics[2].The application of permeation enhancers, enzyme inhibitors, and mucoadhesive agents has demonstrated potential in enhancing the transport and stability of biologics across the intestinal barrier. Additionally, pH-responsive coatings enable targeted release in certain parts of the gut, preventing early degradation in the stomach.Another significant advancement is receptor-mediated delivery, which takes advantage of natural uptake mechanisms in the intestine to assist in the absorption of therapeutic proteins. Innovations like microneedle capsules and smart pills are being investigated for their ability to deliver treatments to specific sites and control their release. Importantly, the approval of Rybelsus (oral semaglutide) for type 2 diabetes marks a major achievement, showcasing the practical viability of oral biologics[5].As research advances, technological breakthroughs are helping us move toward the objective of safely, effectively, and conveniently delivering biologics through oral means[4]. The combination of various approaches holds significant promise for transforming how biological therapies are administered, enhancing patient adherence and outcomes.

PHYSICAL OBSTACLES TO THE ORAL ADMINISTRATION OF BIOLOGICS

The oral distribution of biologics is greatly hampered by a variety of physiological obstacles within the gastrointestinal (GI) tract, all of which contribute to the macromolecules' poor bioavailability[6]. One of the most significant problems is the severe acidic environment of the stomach (pH 1.5-3.5), which can denature proteins and peptides before they reach the absorption location in the intestine[9]. Another significant obstacle is the presence of digesting enzymes like pepsin in the stomach and proteases (trypsin, chymotrypsin, and carboxypeptidases) in the small intestine.Another significant obstacle is the presence of digestive enzymes in the stomach, such as pepsin, and proteases (trypsin, chymotrypsin, and carboxypeptidases) in the small intestine. These enzymes quickly breakdown biologics, reducing their therapeutic efficacy[7]. The mucus layer that lines the GI system serves as both a physical and chemical barrier, trapping and decomposing foreign molecules such as therapeutic proteins. Furthermore, the intestine's epithelial cell membrane, particularly the tight connections between enterocytes, impedes the paracellular transport of big, hydrophilic molecules such as biologics[8].The intestinal

epithelium's restricted permeability reduces the amount of biologics that can be absorbed into the systemic circulation. Oral administration is further complicated by first-pass metabolism in the liver, which can degrade ingested compounds before they have therapeutic effects[10]. Furthermore, individual variations in stomach emptying time, intestinal pH, and motility contribute to drug absorption inconsistency. These physiological hurdles highlight the complexities of developing effective oral formulations for biologics, as well as the necessity for enhanced drug delivery systems capable of protecting, transporting, and releasing biologics at optimal places in the GI

DEFEND THE BIOLOGICAL SYSTEM AGAINST ENZYMATIC AND ACID DEGRADATION.

One of the most difficult issues in oral biologic delivery is preserving them from degradation in the hostile gastrointestinal (GI) environment[11]. The stomach's acidic pH, as well as the presence of proteolytic enzymes throughout the GI system, represent substantial challenges to the stability and integrity of biologic medications like peptides and protein. To address this, a variety of formulation solutions have been devised. Enteric coatings are commonly utilized to protect biologics against stomach acid.These coatings remain intact in the stomach's acidic environment, but disintegrate at the higher pH of the small intestine, where absorption is better. This ensures that the biologic is only released after it passes through the stomach. Encapsulation in nanoparticles, liposomes, or polymeric microspheres creates a physical barrier against enzymatic breakdown. These carriers can protect the biologic from proteases while gradually releasing the medicine to the target location, enhancing its stability and bioavailability.Enzyme inhibitors are another useful technique. Protease inhibitors combined with biologics assist neutralize digestive enzymes such as trypsin and chymotrypsin, inhibiting enzymatic breakdown in the intestine. Mucoadhesive polymers, such as chitosan or carbopol, not only preserve biologics by generating a gel-like barrier, but they also extend their residence duration at the absorption site, so increasing uptake. Furthermore, pH-responsive hydrogels can encapsulate and release biologics in a regulated manner in reaction to pH variations.These protective strategies are essential for preserving the activity of biologics during transit through the GI tract, ultimately enabling more effective oral drug delivery systems[12].

UTILIZE THE ABSORBENT EPITHELIUM TO EXTEND THE BIOLOGICAL CONTACT TIME.

Increasing biologics' contact time with the gastrointestinal (GI) tract's absorptive epithelium is an important method for improving oral bioavailability[15]. Prolonged contact with the epithelial surface improves medication absorption, particularly for big molecules with low permeability, such as proteins and peptides. One of the most effective strategies is to use mucoadhesive polymers like chitosan, carbopol, and alginate. These components bind to the mucus layer that covers the intestinal epithelium, anchoring the drug delivery mechanism and slowing its evacuation by peristalsis[13].This longer residence period allows the biologic to spend more time at the absorption site, resulting in better uptake. Hydrogels and bioadhesive microspheres are also employed to generate a gel matrix when hydrated, which protects the biologic while also improving mucosal adherence and sustaining drug delivery[14]. Furthermore, floating drug delivery devices and gastroretentive formulations can extend gastric residence time, maintaining the drug in the upper GI tract, where certain biologics are more efficiently absorbed.By increasing the interaction time with the intestinal lining, these strategies enhance the chances of biologic transport across the epithelial barrier, thereby improving therapeutic effectiveness through oral administration.

IMPROVED PERMEABILITY OF THE MUCOSAL BARRIER

While the gastrointestinal (GI) tract's mucosal barrier is necessary for protecting the body from hazardous chemicals, it also poses a significant barrier to oral biologic delivery. Tight junctions block the epithelial lining, preventing big, hydrophilic molecules like peptides and proteins from passing through. As a result, increasing the permeability of this barrier is an important method for optimizing biologic absorption when supplied orally[16]. One well researched option is the use of permeation enhancers. These are drugs that temporarily open epithelial cell tight junctions or change the cell membrane, allowing for more paracellular or transcellular transport of biologics.Common permeation enhancers include fatty acids (e.g., sodium caprate), surfactants (e.g., bile salts, sodium lauryl sulfate), and chelating agents (e.g., EDTA). These compounds work by altering membrane fluidity, disrupting lipid bilayers, or interacting with tight junction proteins[17].

Zonula occludens toxin (ZOT) and its synthetic analogs have also been explored for their ability to reversibly modulate tight junctions and enhance paracellular transport.

Additionally, cell-penetrating peptides (CPPs) and nanocarriers can facilitate transcellular transport by promoting endocytosis and intracellular trafficking of biologics across the mucosal epithelium.Importantly, the effects of permeation enhancers must be transient and reversible to avoid long-term alteration of the mucosal barrier, which could result in toxicity or increased susceptibility to infections[19]. These strategies considerably increase the chances of successful oral administration of biologic medications by modulating mucosal permeability in a controlled and reversible manner, making treatment more patient-friendly and effective.

IMPROVE THE BIOLOGIC'S CONTACT TIME WITH THE ABSORPTIVE EPITHELIUM.

One of the most significant drawbacks of oral biologic delivery is their quick transit through the gastrointestinal (GI) tract, which lowers the amount of time available for absorption. Increasing the contact period of biologics with the absorptive epithelium is an important method for improving bioavailability[18]. The longer a biologic is in close proximity to the intestinal lining, the greater its chances of being absorbed into systemic circulation. A important technique is the use of mucoadhesive drug delivery devices. These methods use polymers including chitosan, carbopol, alginate, and polycarbophil, which can bind to the mucus layer of the intestinal wall.This adherence increases the formulation's residence time at the absorption site, allowing for longer-term release and better contact with epithelial cells[20]. Another approach is to create hydrogels and bioadhesive microspheres that

swell in the presence of GI fluids, forming a gel matrix that stays in touch with the mucosal surface. These technologies not only protect the biologic against degradation, but also allow for sustained and targeted drug release. Gastroretentive drug delivery technologies, such as floating tablets, expandable systems, and high-density formulations, are intended to increase the biologic's retention duration in the stomach or upper small intestine, where absorption may be better[22]. This is especially effective for biologics that are better absorbed in the upper gastrointestinal tract.Additionally, enzyme-triggered or pH-responsive formulations can ensure that the biologic is released only when it reaches specific areas of the GI tract, optimizing both stability and absorption[25].

By increasing the contact duration between the biologic and the intestinal epithelium, these advanced delivery systems significantly improve the likelihood of successful absorption, representing a key advancement in the field of oral biologic therapeutics[21].

SURFACTANTS :

Because they contain both hydrophilic and hydrophobic components, they may adsorb on system surfaces, altering interfacial tension and free energy. In addition to temporarily opening epithelial tight junctions, this causes the intestinal epithelial plasma membrane to fluidize, allowing macromolecules to pass through [24]. Surfactants based on medium-chain fatty acids (such as sodium caprate, sodium caprylate, and N-[8-(2-hydroxybenxoyl) amino] caprylate [SNAC]), bile salts, and acylcarnitine are presently the principal candidates used in the creation of oral peptide formulations. The eigen and "gastro-intestinal permeating" technologies (Novo Nordisk) are two examples of these materials-based technologies that are currently in clinical trials[23].Recently, it was announced that a SNAC formulation for oral administration of semilattice (Novo Nordisk), a long acting GLP-1 analogue, had effectively finished its first phase IIIa research for type 2 diabetes mellitus. as it was demonstrated that three oral dosages of semilattice (3 mg, 7 mg, and 14 mg) improved HbA1c levels as compared to a placebo, the 703-person trial's primary objective was achieved. Additionally, there are currently vitamin B12 tablets with high SNAC dosages available on the market [26]. Mycapssa (Chiasma) capsules are currently being studied in three phase III trials across the globe, and they appear to have a lot of potential. The "transient permeability enhancer" (TPE) technology was developed by the Israeli biopharmaceutical company Chiasma and is being used in Mycapssa capsule formulations for the maintenance treatment of adult patients with acromegaly.The active ingredient in this formulation is the peptide octreotide, a somatostatin analogue. TPE technology, which combines pharmaceutical excipients, can improve octreotide's oral bioavailability. This combination produces an oily suspension of hydrophilic particles in a hydrophobic matrix. Octreotide dissolves in the hydrophilic component, along with sodium caprylate and other excipients[26]. Surfactants in this formulation protect the drug from the digestive tract by temporarily expanding tight junctions. It is protected from digestive enzymes, breach the intestinal epithelial membrane, and reach the bloodstream.

PERMEATION ENHANCERS OPENING TIGHT JUNCTIONS.

Because of their poor stability and low permeability across the intestinal epithelium, oral delivery of biologics such as peptides, proteins, and nucleic acids continues to be difficult. One intriguing technique is to use tight junction (TJ)-opening permeation enhancers (PEs) to alter the paracellular route temporarily, allowing macromolecules to flow through the otherwise restrictive intestinal barrier. Recent developments have centered on identifying and optimizing PEs that are both effective and safe[25]. Compounds like medium-chain fatty acids (e.g., sodium caprate), chitosan derivatives, and surfactants have been shown to reversibly open TJs via regulating proteins like claudins and occlusins.Novel synthetic peptides and small compounds targeting specific TJ regulators, like as zonula occludens toxin derivatives, have also showed potential in preclinical studies. Nanotechnology has improved PE delivery, allowing for targeted and persistent TJ regulation. Lipid-based and polymeric nanoparticles containing biologics and PEs can localize TJ-opening activity while reducing systemic exposure. Furthermore, stimuli-responsive mechanisms that activate PEs in response to pH or enzyme levels in the gut provide additional control over TJ opening[27].

IMPROVE THE PERMEABILITY OF THE BIOLOGICAL DRUG OR DRUG DELIVERY SYSTEM.

Biologic medications confront severe hurdles to oral distribution due to their enormous bulk and low permeability across the gut epithelium. Tight junction (TJ)-opening permeation enhancers (PEs) are a possible answer because they temporarily weaken the intercellular connections between epithelial cells, allowing biologics to enter through the paracellular pathway. Recent research focuses on safe and reversible TJs regulation using drugs such sodium caprate, chitosan derivatives, and new synthetic peptides.By temporarily interfering with TJ proteins such occludins and claudins, these enhancers increase epithelial permeability without causing long-term harm[28]. To safely co-deliver biologics and PEs, sophisticated drug delivery systems like as lipid carriers and nanoparticles have been created. By ensuring localized action, these methods reduce toxicity and systemic exposure. TJ-opening PEs greatly increase the oral bioavailability of biologics by improving paracellular transport, opening the door for more efficient, patient-friendly drug delivery methods.

GET BEYOND THE MUCOSAL BARRIER WITH "SMART" EDIBLE DEVICES :

A major obstacle to oral biologic delivery is the gastrointestinal (GI) tract's mucosal barrier, which restricts the absorption and therapeutic effectiveness of biologics. As a result of recent advancements, "smart" ingestible gadgets have been created that use controlled, targeted delivery methods to get around or beyond this obstacle[29]. These devices are designed to provide site-specific release in the colon and shield biologic medications from severe stomach conditions. Many have stimuli-responsive triggers, pH-sensitive coatings, or microneedles that only initiate drug release when the GI environments are at their ideal levels.Certain sophisticated techniques avoid the mucosal and epithelial barriers by using microneedles to safely inject biologics into the gut wall. To ensure accurate drug release and absorption, other smart devices use biosensors and electronics that react to temperature, pH, or enzyme activity.

[30] that further improve permeability, these devices occasionally also have mechanisms that temporarily disrupt mucus or open tight junctions.These systems are becoming more feasible thanks to the combination of materials science, biomedical engineering, and microfabrication; multiple prototypes have demonstrated encouraging preclinical and early clinical outcomes. A state-of-the-art method of oral biologic delivery, smart ingestible devices promise increased patient compliance, decreased dose frequency, and greater
Peristalsis compresses the drug reservoir in hollow microneedles, causing the medication to be released via the needles[23]. The medication is formed into the solid microneedles. When these pierce the tissue and separate from the tablet, the needle is left to deliver the medication in a regulated way.

A recent landmark study reported a drug delivery system that resembles the leopard tortoise (Stigmochelys pardalis) — a tortoise with a steeply domed shell that it uses to self-orient should it roll onto its back. This innovative oral delivery system, known as the "self-orienting millimetre-scale applicator" (SOMA), uses the same shape and low centre of gravity to physically insert a biodegradable microneedle through the stomach mucosa for systemic administration of biotherapeutics . When the SOMA was loaded with human insulin and administered to swine, a blood-glucose lowering effect was observed, indicating successful drug delivery.

ABILITY TO CLINICALLY TRANSLATE THE DELIVERY STRATEGY FOR ORAL BIOLOGICS.

The need for non-invasive, patient-friendly injection substitutes has fueled a rapid advancement in the clinical translation of oral biologics delivery techniques. Strategies like protected delivery systems, clever ingestible devices, and tight junction-opening permeation enhancers (PEs) have demonstrated encouraging outcomes in increasing the bioavailability of proteins and peptides. The approval of oral semaglutide, a GLP-1 analog administered with the absorption enhancer SNAC, is noteworthy since it shows that oral biologic delivery is feasible and clinically viable.As they advance through preclinical and early clinical studies, emerging technologies like as stimuli-responsive carriers and capsules coupled with microneedles are demonstrating their safety, effectiveness, and reproducibility. Important obstacles still need to be overcome, though, such as guaranteeing mucosal safety over the long term, uniform absorption in a range of patient demographics, and scalable production. Additionally, regulatory pathways are changing to make room for these new systems.Despite these hurdles, continued interdisciplinary research and investment are positioning oral biologic delivery strategies for broader clinical adoption, potentially transforming chronic disease management.
this situation, it will be crucial to carefully assess the biologic, disease area, and patient group to employ these drug delivery systems[25].

CONCLUSION

Recent advances in the oral delivery of biologics have significantly expanded the potential for more patient-friendly treatment options. Innovations in drug formulation, such as nanoencapsulation, mucosal permeation enhancers, and advanced oral delivery systems like micro- and nanoparticles, have overcome many of the traditional barriers to oral biologics, including instability in the gastrointestinal tract and poor absorption. Technologies such as enzyme inhibitors, liposomal carriers, and pH-sensitive polymers are showing promise in enhancing the bioavailability and efficacy of biologic drugs delivered orally.Furthermore, the integration of cutting-edge technologies like precision medicine and smart drug delivery systems holds great potential for the future. These developments not only offer an opportunity to improve patient compliance and reduce the need for injections, but they also contribute to personalized treatment strategies for complex diseases. However, challenges related to scalability, regulatory hurdles, and cost remain, and more research is required to bring these advances to widespread clinical application. Despite these challenges, the field is progressing rapidly, and the future of oral biologic delivery looks promising.

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