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Bridging the Gap: Investigating the State-of-the-Art Approaches in Oral Biologic Delivery and Their Role in Redefining Therapeutic Possibilities

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Abstract

Biopharmaceutical medications that originate from biological sources and processes are known as biologics. Biologics are now the most promising medications for oral use in treating a variety of illnesses. These illnesses may involve problems with inflammation and metabolism. It has been established that the most practical way to provide medication is by oral delivery of biologics. Due to the simplicity of taking doses, patients are observed to be directed towards the oral drug, demonstrating its great effectiveness. Even though biologicals are the most promising medicine, oral delivery of these drugs still faces numerous challenges because of a number of extremely strict limitations. The two major obstacles are the sensitivity and the difficulty of delivering the biologics through the gastrointestinal tract. Because oral administration of biologicals has been shown to be crucial for achieving the desired long-term effects from the treatment, it is the most researched topic and continues to attract the attention of several researchers. Since it is more convenient for patients, taking medications orally is preferred; however, biologics cannot currently be administered orally. Multiple barriers are present in the gastrointestinal tract due to its physiological role, which restricts the absorption of complex macromolecules into the body after intake. Because biologics are relatively large molecules, they have very limited permeability across the intestinal mucosa in addition to being exceedingly vulnerable to the harsh environment of the digestive tract. The history of research on oral delivery of biologics is extensive, and the recent surge in biologics has further intensified this body of work. The primary physiological obstacles to oral biologic delivery are outlined in this article along with many research approaches that may be used to facilitate or enhance oral biological delivery.

Keywords: Biologics, intestinal mucosa, permeability, oral delivery, gastrointestinal tract, macromolecules

Introduction:

Medications made from living things are referred to as biologics; these can include proteins, peptides, and vaccinations. It has been about 300 years since biologics were introduced into the medical field as a means of treating patients. The oral delivery of biologicals is to be studied for various reasons and requirements. It is one of the most auspicious ways of oral delivery of the antibiotic[1]. Biologics have drastically revolutionised the treatment of many ailments, including diabetes, cancer, and inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease (IBD). Although they have been used in clinical settings for a long time—nearly 100 years, in the case of insulin—their development and application have risen dramatically over the last 20 years as a result of biotechnology developments and new knowledge about biology and disease processes. Biologics made up eight of the ten best-selling medications worldwide in 2018 (as measured by US dollars)[2] . The research concerning the history of oral biologics has rich and detailed information available. Biologics are completely different from traditional medicines in form of their structure, chemical formula, efficacy, storage, administration, and cost. Biologics are known to be extremely complex and sensitive to the environment of the digestive tract. Hence, they are ought to be kept in an optimum environment for safety. Biologics are said to be the most preferred alternate traditional medicines due to their convenience. There are several types of biologics being delivered from the oral passage in the human body. Biologics are distinct from "conventional" medications manufactured from chemicals in numerous aspects, which have an impact on cost, clinical effectiveness, production, and administration. In contrast to small-molecule medications like aspirin, biotherapeutics often possess a substantially larger molecular weight and an intrinsically diverse structure. Biologics are huge, complex molecules that are very susceptible to the chemical and physical environments of the gastrointestinal (GI) tract. Because of their sensitivity, biologics are currently administered through injection, with a few exceptions.On the other hand, the most practical and recommended way to

provide medication is orally[3]. There are extra benefits of consuming insulin rather than injecting it. For example, oral insulin delivery more closely reflects the physiology of endogenous insulin released by the pancreas, lowering systemic insulin levels and reducing the likelihood of hypoglycemic episodes and weight gain difficulties[4]. Insulin administered orally also lowers costs and problems associated with needle use.

It is important to know about the advancements, changes, and technological challenges being occurred in the way of oral conveyance of biological drugs to comprehend these insights, this paper will talk about advancements, challenges, and the future predictions pertinent to oral delivery of biologics. Further, it will talk about the various routes of oral delivery administration, among them the major one is, the gastrointestinal tract.

Because of their unique problems, biologicals like vaccines are particularly interesting in the context of medication delivery. Most of the vaccines that are currently available are given by intramuscular injection[5]. The chief causes of this are the harmful effects of proteases in the GI tract and the limited penetration of macromolecular biopharmaceuticals over the mucosal barrier in the non-parenteral route[5]. Drugs can also be successfully stored in a range of biological settings, and the release behaviour in topical injections can be precisely controlled using silica and polymer mesoporous structures[7]. However, as compared to subcutaneous or IV injection, intramuscular administration is not the optimal technique of delivering peptides or proteins. This is mostly owing to the reduced immunogenicity and bioavailability that IM treatment provides[8]. Despite the fact that intramuscular vaccination (IM vaccination) is a popular commercial treatment and that the local depot at the injection site can readily trigger the immune response in this system, this delivery method is not the ideal option for peptide/protein delivery because of the potential for drug aggregation[9]. Biologics being declared as the modern solution to the diseases, such as bowel disease, inflammatory disease, diabetes, and cancer is provided with higher importance. It has been studied that in 2018 almost eight out of ten medications sold in America appeared to be Biologics. With the amalgamation of the recent advancements, the research of oral delivery of biologics is increasing the clinical drug technologies. Several advancements were made to enhance the efficiency of the medications. The first and foremost advancement was to protect biologics from acidic and enzymatic degradation. It occurred by having a collaboration of proteins and peptides with inhibitors, which helps to modify the chemical structure of the biologics and improve the stability of the fluids in the gastrointestinal tract. This strategy of advancement has been made possible by an innovation process of cyclization approach. Another major advancement is the increased time of the biologic with the absorptive epithelium, this helps in the prevention of luminal loss from the biologic and is said to be consisting vital enhancement of absorption of the medicine in the gastrointestinal tract. The third advancement made for the betterment of oral biologic delivery is making the mucosal barrier highly permeable. This strategy improves and enhances the oral bioavailability of the biologics due to the modification of the intestinal mucous barrier and epithelial barrier. It further helps in the diffusion of the bigger molecule of biologics. The fourth advancement in the field of oral delivery of biologic is, to make the biologic delivery mechanism more permeable. In short, it describes how the biologic's oral delivery mechanism facilitates improved drug absorption within the body, enhancing the medication's effectiveness and efficiency and reducing the incidence of disorders in the body. Success and other breakthroughs have also been demonstrated in biologics. In the years 2015–2018, biologics made up about 30% of all medications authorised by the US Food and Drug Administration.Today almost 60 peptides are being approved by the administration; this is twice the number previously being approved. The table below shows the oral administration overview of the biologics[10]. The growing success of biologics within days is expected to be dedicated to the safety and regulation of biologics. These advancements are successful and are proven to be making biologics the most promising drug among all the conventional medications.

Oral biologic delivery is hampered by physiological factors

The various physiological barriers found in the gastrointestinal tract (GIT) provide a significant obstacle to the clinically relevant administration of oral biologics. These barriers are intended to stop the body from absorbing foreign substances, such dangerous bacteria or their metabolites, from the external environment. For instance, the lumen of the stomach (Figure 1). The crucial chemical barrier is the pH-induced proteolysis of proteins into their individual amino acids, dipeptides, and tripeptides. Biochemical barriers include endopeptidases, which are proteolytic enzymes present at the brush border membrane, pepsin, trypsin, and chymotrypsin found in the gut lumen, and the efflux pump. The P-glycoprotein [11]. But the largest and most important barrier to the absorption of biologics is the gut epithelium. Although the intestinal epithelium is only one cell thick, the cell membrane barrier that faces the lumen is nearly continuous due to the way the cells are arranged. Moreover, the mucus layer above the epithelium, which varies in thickness depending on the gastrointestinal region additionally have the capacity to act as a barrier, preventing biologics from diffusing to the underlying epithelium [11]. Basement membranes are thin, specialised sheets of extracellular matrix that lie between the epithelia and the connective tissue. They can limit systemic absorption by preventing macromolecules from penetrating the area beneath the epithelium [12,13]. The less than 1% oral bioavailability of biopharmaceuticals is mostly due to these issues[14].

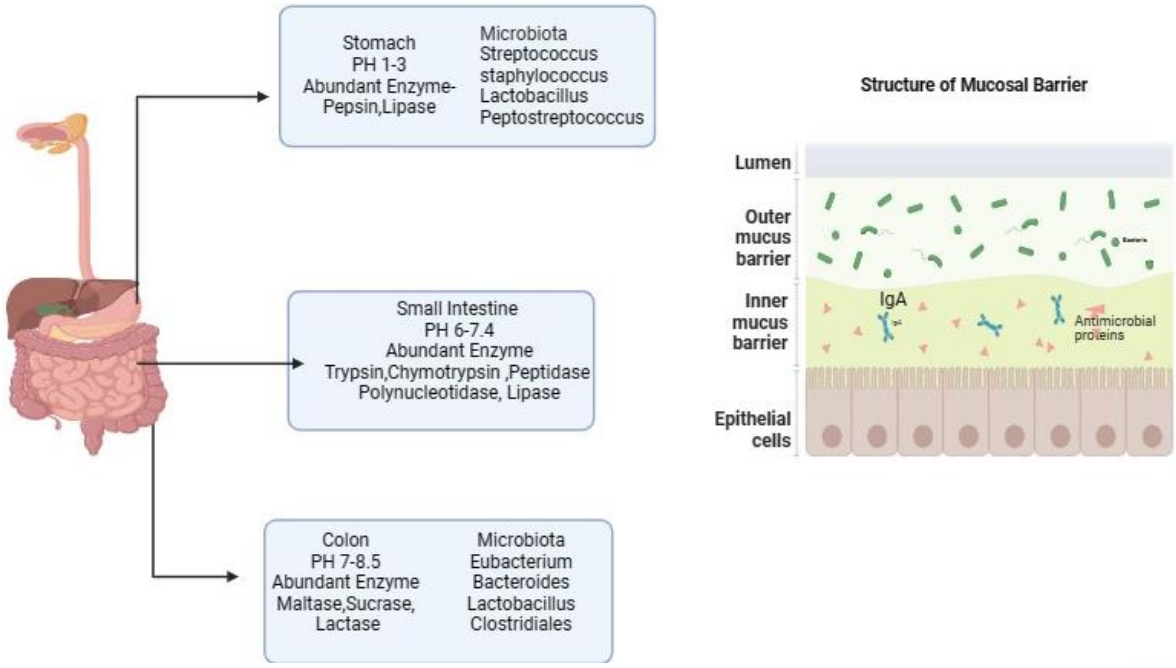

Figure1: Physiological barriers that stop biologics from being absorbed in the stomach and gut

Techniques to enhance the oral administration of biologics

1. Protect the biologic against enzymatic and acid breakdown

Reducing acid degradation is one way to make biologic medicines more bioavailable. Delivery inside enteric-coated systems is one way to accomplish this; although these systems are well-established, they won't be covered in this study[15]. Protease inhibitors and protein and peptide medications together can shield biotherapeutics from the proteolytic enzymes present in the gastrointestinal tract. Certain biologics, especially peptides, can also have their chemical structures changed to increase their stability in GI fluids. Using the "cyclization" approach is one approach that might be used for this [16]. Because some biologics have higher intrinsic physicochemical stability against enzymatic breakdown in the GIT, they might be appropriate for oral administration. Two instances of anti-body fragments obtained from sharks and llamas are being investigated for their potential as oral delivery systems for treating inflammatory bowel disease by inhibiting the growth of tumour necrosis factor-alpha[17]. It is imperative to underscore that protecting the biologic drug from acid and enzymatic degradation is a necessary precondition. Ensuring that this requirement is met is also a requirement for the strategies that follow, which are designed to improve oral administration of biologics.

2. Extend the biologic's duration of contact with the absorptive epithelium

This approach seeks to avoid luminal loss of the medicine by providing it at high concentrations in close proximity to the absorptive epithelium—a crucial factor to take into account considering the length of the gut. In general, polymers that interact with mucus both ionically and non-ionically are referred to as "mucoadhesive" substances. They may contribute to better absorption by accomplishing this by extending the drug's residence time at the absorption site[18]. As opposed to artificial mucoadhesive polymers, which consist of polyacrylic acid polymers, cellulose derivatives, polyethylene glycol, polyethylene oxide, polyvinyl pyrrolidone, and polyvinyl alcohol, natural mucoadhesive polymers consist of guar gum, xanthan gum, pectin, gelatine, sodium alginate, and chitosan. Numerous of these materials have been explored for oral biologic administration, with differing degrees of success[19]. Utilizing a mucoadhesive "transdermal patch-like" method, oral delivery of the therapeutic polypeptide salmon calcitonin (sCT) can be improved[20]. Gastro-resistant firm gelatin capsules are used to deliver this system, which is based on mucoadhesive polymers such carbopol 934, pectin, and sodium carboxymethylcellulose. Analogous muco-adhesive patches have been studied for oral delivery of insulin and exenatide. The system showed a notable improvement in intestine sCT absorption in vivo. A 42% drop in blood glucose was observed in the rat jejunum following surgical implantation of these systems; no similar impact was observed in the group that received insulin solution treatment (control). When exenatide and insulin were administered intraperitoneally, their relative bioavailability rose significantly (by 80 and 13-fold, respectively) [21]. Though this method may not be as successful with larger biologics (such as monoclonal antibodies), mucoadhesive systems have demonstrated promise in both in vitro and in vivo oral administration of biologics. To increase bioavailability in a way that is clinically significant, it might not be sufficient to simply prolong the biotherapeutic's residence time at the absorbent surface. This makes sense given that hydrophilic drugs have a limited ability to cross the intestinal epithelium at molecular weights orders of magnitude higher than 500Da. Furthermore, the

potential effects of intestinal mucus turnover on these systems' operations remain unclear [22]. Additionally, there could be potential issues with application of such systems in diseases associated with mucus defects (e.g. IBD).

3. **Increase the permeability of the mucosal barrier**

The most researched methods for increasing the oral bioavailability of biologics are these ones. Both the epithelium barrier and the intestinal mucus barrier are modifiable. Mucolytics, or drugs that break down mucus, include N-acetylcysteine, which can be used to change the mucus barrier and enhance the diffusion of biologics with big molecules. But, since the epithelium frequently acts as a rate-limiting barrier, altering the epithelium as opposed to the mucus is typically more beneficial. Numerous chemicals that open epithelial tight junctions, such as surfactants, can alter the epithelium barrier as chemical absorption enhancers [23]. There are hydrophilic and hydrophobic components in surfactants. Adsorbing onto a system's interfaces, these materials can change the interfacial free energy and tension, resulting in fluidisation of intestinal epithelial plasma membrane, but also transient opening of epithelial tight junctions, thereby facilitating permeation of macromolecule[24]. The primary candidates now being used in the production of oral peptide formulations are surfactants based on medium-chain fatty acids (e.g., sodium caprate, sodium caprylate, and N-[8-(2-hydroxybenxoyl) amino] caprylate [SNAC]), bile salts, and acyl carnitines [25]. After decades of research in this field, numerous compounds, including surfactants, have been found to be capable of opening epithelial tight junctions. Since the medication can escape penetrating the epithelial cells and can instead be present in an environment rich in enzymes during the absorption process, opening the epithelial tight junctions may be a good strategy to increase the permeability of the intestinal epithelium.

4. Increase the permeability of the biologic modification or drug delivery method

Depending on the biologic's characteristics, the molecule can be changed chemically to provide it the ability to penetrate epithelial cells. Attaching the biotherapeutic to another molecule that has the same ability to pass the intestinal epithelium can also help boost its ability to do so. Usually, a particular receptor expressed in the intestinal epithelial cells allows this "transport-enabling" molecule to pass through the intestinal epithelium. Biotechnology-mediated fusion technologies or chemical attachment (conjugation) can be used to join the two entities. Biological transport pathways that are employed by other peptides or proteins to facilitate their passage across the epithelium are instances of molecules that facilitate transport [26]. Researchers have combined biotherapeutics with intestinal barrier-crossing drug carrier systems in addition to modifying the biologic to increase its chance of doing so[27]. For this purpose, biologic carriers are usually based on biodegradable polymeric nanoparticles, which offer several benefits, and are typically nanometer in size. For instance, some nanoparticles provide the medicinal medicine with defence against the GIT's acid and enzymes. Furthermore, by targeting particular receptors found on the surface of intestinal epithelial cells, targeted drug administration can be accomplished. But like large molecule biologics, most of the time intestinal mucosa absorbs nanoparticle carriers poorly. Nanoparticles are unable to pass through the intestinal epithelium and may diffuse poorly in intestinal mucus. As a result, For the oral delivery of biologics, certain substances are designed to bind to biological transport receptors produced in intestinal epithelial cells on the surface of drug carriers based on nanoparticles. Numerous research groups have investigated such delivery strategies, which include nanoparticles that take advantage of the intestinal epithelial transport channels for vitamin B12 and immunoglobulin G (IgG)[28]. The human intestinal epithelium has the neonatal Fc receptor (FcRn), a biological transport system that has demonstrated significant promise for intestinal nanoparticle transport. FcRn aids in the intestinal transport of serum albumin and IgG. Potential for oral insulin administration was demonstrated by FcRn-targeted polymer nanoparticles. Compared to nanoparticles not directed towards the FcRn system, these orally delivered nanoparticles in mice had a greater absorption efficiency as they passed through the intestinal epithelium and entered the bloodstream. When compared to the control group of mice (FcRn-knockout animals), the insulin-containing nanoparticles caused a longer hypoglycaemic impact in mice expressing the receptor. FcRn-targeted polymer nanoparticles for exenatide oral administration were investigated in another study [29].

In comparison to unmodified nanoparticles, these systems translocated across the intestinal epithelium more quickly and extensively. When exenatide was delivered by these nanoparticles as opposed to subcutaneous injection, the hypoglycaemia lasted longer. The development of nanomedicine-based techniques confronts various hurdles, despite the potential benefits and encouraging preclinical research results: limited therapeutic loading capacity is a potential drawback for nanoparticle-based carriers, especially when it comes to bigger biologics like monoclonal antibodies. Delivery capacity may also be a problem, since the biological pathways that these systems often use have limited trans-port capacities[30]. In the presence of extremely complex intestinal biofluid, the complex nanocarriers may experience significant breakdown or modification in the gastrointestinal tract. The primary concern pertains to the attachment or adsorption of substances that are typical components of intestinal biofluid, such as proteins and peptides, on the surface of nanocarriers. This process affects the nanocarriers' capacity to bind to biological receptors and employ these systems for transporting material across epithelial cells.

Novel developments in biological delivery

Ingestible instruments for gastrointestinal biological distribution

Ingesting "smart" devices help improve the intestinal absorption of biologics by using ultrasound and microneedles, among other techniques, in addition to shielding the treatment from the harsh environment of

the gastrointestinal tract. Preclinical research has yielded positive results thus far, according to Rani Therapeutics, the startup developing the microneedle oral delivery technique in the United States[31]. The device works by injecting the medication into the small intestine through a capsule that is intended to stay intact in the stomach (see Figure 2). This method is painless and has shown good insulin bioavailability, comparable to or better than subcutaneous injections since the stomach mucosa lacks pain receptors. The benefit of this approach is that it can potentially transport low-to-medium molecular weight biologics along with larger biologics, such as antibodies. As seen in Figure 2, the capsules are initially coated with a pH-responsive substance to aid in swallowing. When the tablet reaches the desired location in the GIT, the coating melts and releases the microneedles [32]. The term "microneedle oral delivery technology" refers to a range of methods that use microneedle-based devices to deliver medicinal biologics orally. These technologies take advantage of the advantages of microneedles, which are minuscule needles with a typical length of micrometres to millimetres, to pierce the GI tract's mucosal barriers and aid in drug absorption. The following categories of microneedle oral delivery technology for biologicals:

Solid Microneedles: Solid microneedles are microscopic needles made from materials such as silicon, metal, or biodegradable polymers. These needles are designed to penetrate the mucosal barriers of the GI tract upon oral administration, allowing for the delivery of therapeutic biologics directly into the systemic circulation or local tissue. Solid microneedles can encapsulate biologic payloads or be coated with biologics for controlled release upon insertion into the intestinal mucosa.

Hollow Microneedles: Hollow microneedles feature a central lumen or channel that allows for the delivery of liquid formulations, including biologicals, through the needle tip. These microneedles can be fabricated from materials such as glass, polymers, or metals and are used to administer biologics directly into the GI tissue or systemic circulation upon penetration of the intestinal mucosa. Hollow microneedles offer the advantage of delivering precise doses of liquid biologics with minimal tissue damage.

Dissolving Microneedles: Dissolving microneedles are composed of biocompatible polymers or sugars that dissolve upon insertion into the GI tissue, releasing encapsulated or coated biologic payloads. These microneedles can be fabricated with or without a hollow structure and are designed to rapidly dissolve within the mucosal environment of the tract, facilitating the release and absorption of biologics into the systemic circulation or local tissue.

Degradable Microneedles: Degradable microneedles are designed to dissolve or degrade after administration, allowing for the controlled release of drugs or bioactive molecules into the body. These microneedles are typically made from biocompatible and biodegradable materials such as polymers or sugars. Biodegradable polymers like polylactic acid (PLA), polyglycolic acid (PGA), or polylactic-co-glycolic acid (PLGA) are commonly used for fabricating degradable microneedles.

Bioresponsive Microneedles: Bioresponsive microneedles are designed to respond to specific biological cues or changes within the body, triggering drug release or other therapeutic actions. These microneedles often incorporate components that can detect pH changes, enzyme activity, or specific biomarkers indicative of disease states. Bioresponsive microneedles can be engineered with smart materials or drug-loaded nanoparticles that respond to changes in the local environment.

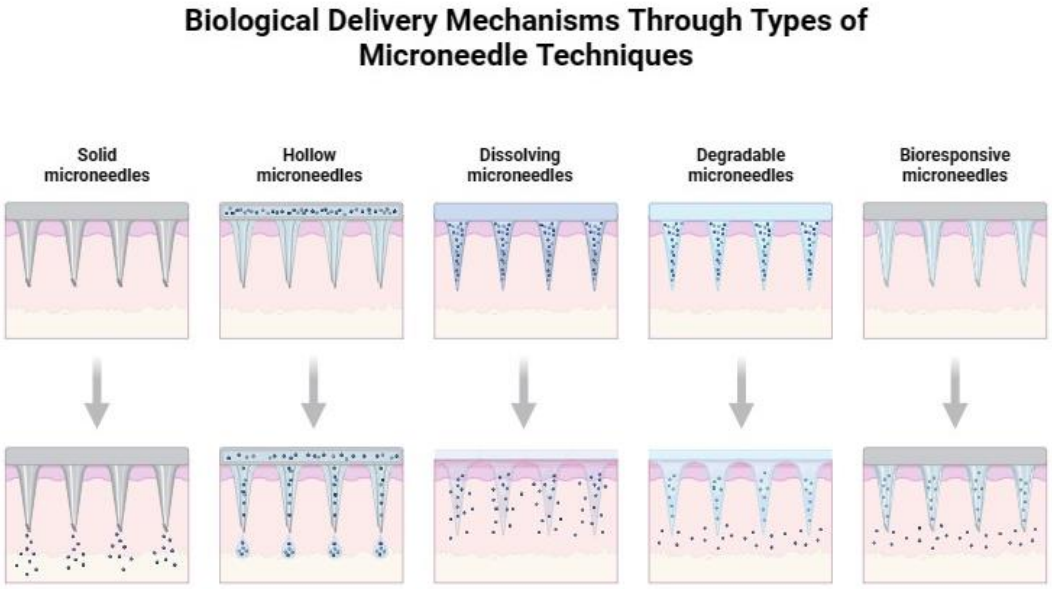

Figure 2: Different types of microneedle oral delivery technology for biologicals.

When a system has hollow microneedles, peristalsis compresses the drug reservoir, causing the medication to be released through the needles. When using a system with solid microneedles, the medication is formulated

into the needles, which break off from the pill and enter the tissue. This allows the needle to release the medication in a regulated way according to the needle formulation [32].

Possibility of clinical application of oral biologics delivery techniques

Although research into oral biologic delivery devices is still in its early stages, these devices are showing great promise. Although several of the drug delivery techniques covered above have demonstrated promise and good outcomes in vivo and in vitro, patient usage of these techniques has not yet occurred. Sadly, safety and efficacy are frequently at odds with each other when it comes to many of the delivery methods covered above; as a result, it is unlikely that these tactics will ever enter the clinic. Moreover, it is widely recognised that most permeation enhancers utilised in the ongoing oral peptide clinical studies result in harm to the small intestine's epithelium. Chronic repeated dosing of such absorption enhancers may be able to override the body's repair systems, even though tissue damage is frequently transient and reparable. A less risky option would be to use biological transfer mechanisms to improve the intestinal absorption of biologics and transport them without causing tissue damage. These techniques may, however, be more effective when used with potent biologics because to their likely limited capacity. While efficacy does not appear to be a problem, such devices must unambiguously demonstrate safety upon repeated administration in humans. Furthermore, these technologies are anticipated to be expensive in the short- to medium-term, even though their precise costs are currently uncertain. Because of this, it will be essential to carefully consider which biologic to use with these drug delivery systems, as well as which disease area and patient population.

Clinically approved oral vaccines

Clinically approved oral vaccines (see Table 1) represent a groundbreaking advancement in medical science, offering a convenient and effective way to protect against a variety of infectious diseases. Unlike traditional injectable vaccines, which require needles and healthcare professionals for administration, oral vaccines can be self-administered and don't involve the discomfort associated with injections. This makes them particularly suitable for mass vaccination campaigns, especially in resource-limited settings where access to healthcare infrastructure may be limited [33].

Several oral vaccines have been clinically approved to prevent diseases caused by bacteria and viruses. One of the most well-known examples is the oral polio vaccine (OPV), which has played a critical role in the global effort to eradicate polio. Live poliovirus strains that have been weakened are included in OPV, which encourages the body to create antibodies without actually spreading the disease. Through widespread vaccination campaigns, OPV has significantly reduced the incidence of polio worldwide [34].

Another notable example is the oral cholera vaccine, which provides protection against cholera, a waterborne bacterial infection that can cause severe diarrhoea and dehydration. Oral cholera vaccines contain killed cholera bacteria or parts of the bacteria that induce immunity without causing illness. These vaccines have been instrumental in controlling cholera outbreaks in endemic regions and are recommended by the World Health Organization (WHO) for use in areas at high risk of cholera transmission [35].

Rotavirus is another infectious agent targeted by oral vaccines. Rotavirus vaccines, administered orally, safeguard against a prevalent factor that causes severe diarrhoea in young children and infants. These vaccines have been shown to significantly reduce the incidence of rotavirus gastroenteritis and related hospitalizations, leading to improved child health outcomes [35].

In recent years, researchers have also made significant progress in developing oral vaccines for other diseases, such as typhoid fever and norovirus gastroenteritis. These vaccines are undergoing clinical trials to evaluate their safety and efficacy, with promising results thus far.

Despite their numerous advantages, oral vaccines face certain challenges, including issues related to stability, storage, and the need for multiple doses to ensure adequate immunity. Additionally, Certain oral vaccines might not be appropriate for those with specific medical disorders or weakened immune systems.

Table 1: Clinically approved oral vaccines

Vaccine Name	Disease Targeted	Description
Rotavirus vaccine	Rotavirus infection	Protects against rotavirus, a frequent factor in severe diarrhoea in young children and infants. Administered orally in several doses.
Oral polio vaccine	Poliovirus infection	Contains weakened forms of poliovirus strains to provide immunity against polio. Given orally in multiple doses.
Cholera vaccine	Cholera	Provides immunity against cholera, a bacterial infection causing severe diarrhoea and dehydration. Administered orally in one or two doses.
Typhoid vaccine	Typhoid fever	Protects against Salmonella typhi, the bacterium causing typhoid fever. Available in oral and injectable forms. Oral vaccines are administered in multiple doses.
Oral cholera vaccine (Shanchol)	Cholera	Another type of oral cholera vaccine, similar to other cholera vaccines, administered orally to provide immunity against cholera.

These are just a few examples of clinically approved oral vaccines. There may be others available in specific regions or for particular diseases. Always consult with a healthcare professional for advice on vaccination.

Conclusion

Although research on oral biologic delivery has advanced significantly, it has not yet had a major clinical impact. The safety of drug delivery strategies has typically been linked to the absence of progress in clinical translation in this area, which is partially due to the extremely effective physiological barriers in the GIT. But new discoveries in materials science and a deeper understanding of physiological limitations are driving progress in this field and will probably lead to the clinical implementation of oral biologic administration. The rapid expansion and authorization of biologics for use in clinical settings has transformed medication delivery. It has been moved from the traditional way to the modern oral way. By adopting new tactics and meeting all requirements, the clinical representatives have been able to overcome obstacles resulting from the transfer of medication delivery from conventional to traditional methods. In order to improve the absorption of biologics, the field of biologics has contributed by analysing and assessing the requirements for injectable storage, diffusion, permeability, and residence time. Research and studies on the topic of oral biologic delivery have made a significant contribution to the advancement of medication. Psychological barriers' high efficacy in gastrointestinal tract in approach to safe delivery has also been studied in the paper to analyse the safe approaches. The amalgamation of advancements, challenges and future of biologics has played a vital role to make it a promising drug.

Conflict of Interest

There is no conflict of interest between authors.

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