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A Comprehensive Review on Overcoming Barriers, Challenges, and Future Perspectives of Oral Biologic Drug Delivery

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A B S T R A C T

oral delivery of biologics poses significant role owing to the protective and complex nature of the gastrointestinal (GI) tract. they are large, sensitive macromolecules that can be degraded by digestive enzymes and are not easily permeable through the intestinal mucosa. they previously used to treat chronic diseases like metabolic, inflammatory, and age-related diseases, oral delivery recently begin after decades of research. The intestinal barrier challenging to drug absorption, but some biological agents penetrate intestinal lining on a daily basis. This review describes physiological barriers, recent research approaches to overcome them, and the normal physiology of the GI tract, mechanisms of absorption, assessment and also provides examples from recent clinical trials. The article ends real-life applications and future directions for oral biologics.

Keywords: Biologics, mucosal barrier, Intestinal Epithelium**,** Surfactants, Biodegradable polymeric nanoparticles, Insulin

1.Introduction:

Biologics are medications that contain living organism products such as recombinant proteins, peptides, and vaccines used for the treatment of various diseases like cancer, rheumatoid arthritis, and inflammatory bowel disease (IBD). Biologics have been in medicine almost a full 100 years. in the case of insulin their discovery and application have quickly expanded during the past, due to advances in biotechnology and expanding understanding of biology and disease processes, during the last twenty years. Seven out of the top ten best-selling medicines in the world in 2023 were found to be biologics. Biologics differ from chemically synthesized drugs and especially in terms of relating to the administration, production, related costs, and therapeutic effectiveness of other traditional medicines. Biologics tend to have higher molecular weights and an intrinsic heterogeneous structure. Biologics are big and sophisticated molecules with delicate sensitivity to physical and chemical aspects of GI environment, save and except few cases, biologics today are administered by the route of injection due to the sensitivity factor. [1,2]

2.Physiological Barriers to the Oral Uptake of Biologics through GIT:

The oral delivery of biologics encounters several physiological and chemical barriers within the gastrointestinal (GI) tract. The major issues are: enzymatic degradation (proteolysis) due to changes in pH, a dense intestinal epithelium, and protective mucus, all of which decrease the absorption of the drug. Basement membranes likewise limit macromolecule penetration. Furthermore, efflux transporters, digestive enzymes, and the acidic nature of the stomach all reduce drug stability and uptake. Although duodenum and jejunum regions are better absorbed due to better surface area, the ileum's enzyme-rich brush border and speed of GI motility greatly limit drug residence time within the small intestine. Overall, the combination of all factors results in almost all biologics having less than 1% oral bioavailability. [1]

3. Physiological barriers to biologics absorption in the intestine:

In the stomach, physiological barriers such as gastric acid and digestive enzymes can affect the systemic absorption of biologics following oral administration. In small intestine hydrophilic molecules prevents the penetrate the intestinal epithelium and mucus prevents macromolecules from diffusing freely. additional limitations Even after crossing the intestinal wall, biologics face more hurdles like the tiny blood vessel lining and a dense support layer called the basement membrane, which make it harder for them to enter the bloodstream.[2]

Just like small molecule drugs, the oral delivery of biologics is challenged by several physiological barriers. The stomach is a serious challenge for protein based on drugs due to acidic pH, and digestive enzymes will degrade virtually all protein-based drugs. In the small intestine, it is hydrophilic and large biologics that have difficulty traversing the epithelial lining, and mucus perpetrates traps molecules large enough to avoid diffusion. Once biologics

successfully breach the intestinal wall, there are other barriers to contend with which includes the capillary endothelium, and the extracellular matrix of the basement membrane limit the potential of biologics to enter systemic circulation.[1]

4.Approaches to Improve Oral Delivery of Biologic Drugs:

1. Enteric-Coated Delivery Systems: Medications that are administered orally are coated with a polymer enteric-based coating measure to control the acid degradation time period against modifying the drug dissolution or action within the stomach.

2. Chemical Modification of Biologics: The molecular structure of biologics, mainly peptides, can be manipulated into varying degrees of stability, particularly in gastrointestinal fluids.[2]

3. Use of Naturally Stable Biologics

Certain types of biologics are more likely to withstand denaturation during digestion, for instance, antibody fragments derived from either sharks or llamas show a greater degree of resistance to digestive enzymes. Llama antibody has the potential for oral formulations of therapies, such as anti-TNF-α therapies for inflammatory bowel disease (IBD).[3]

5.Prolonging Contact with the Intestinal Epithelium:

Another method is to maximize the time that the biologic is in contact with the intestinal lining, which maximizes the absorption by the Use of Mucoadhesive Polymers. These polymers could adhere to the mucus layer in gut, and thus slow the drug's transit time and extend the time at the absorption site. Natural mucoadhesive Polymers like Chitosan, pectin, gelatine, sodium alginate, guar gum, and xanthan gum and the Synthetic mucoadhesive Polymers are Derivatives of cellulose, poly (acrylic acid), poly (ethylene glycol), poly (ethylene oxide), poly (vinyl pyrrolidone), and poly (vinyl alcohol) are more effectiveness [27]. Many of these were studied for oral delivery of biologics and include variable results. A mucoadhesive patch-like system utilizing polymers (Carbopol 934, pectin, sodium carboxymethylcellulose) within gastro-resistant capsules have shown to significantly enhance the oral absorption of biologics such as salmon calcitonin, insulin, and exenatide in animal studies. Despite positive results including significant glucose lowering and increased bioavailability challenges remain for large biologics, such as monoclonal antibodies including limited intestinal permeability, unclear effects of mucus turnover, and complications with mucus diseases, such as IBD.[3]

6.Make the mucosal barrier more permeable:

Increasing the oral bioavailability of biologics will involve addressing two main barriers, the intestinal mucus and the epithelial barrier.[1] While mucolytic drugs, like N-acetylcysteine, can promote diffusion by breaking up the mucus barrier the epithelial layer is usually the biggest barrier to overcome. The epithelial layer can be modified with the addition of certain chemical absorption enhancers like surfactants that act by opening the tight junctions between the epithelial cells.

Surfactants have both hydrophilic and hydrophobic components, allowing them to interact with the cell membranes and thus increase permeability. There are many types of surfactants including common ones like medium chain fatty acids (i.e., sodium caprate, caprylate, and SNAC), bile salts, and acyl carnitines[2]. Many companies are developing technologies using surfactants: Novo Nordisk has developed oral formulations using SNAC, one being a GLP-1 analogue (semaglutide) for patients with type 2 diabetes which demonstrated beneficial outcomes in a large Phase III clinical tril.Chiasma's Mycapssa capsules utilize Transient Permeability Enhancer (TPE) technology to deliver octreotide, a somatostatin analogue. The formulation utilizes a combination of surfactants and other excipients that form a protective matrix which temporarily opens the tight junctions to improve absorption of the drug. All the preliminary data and ongoing clinical outcomes show great promise in providing successful oral delivery of injectable biologics.[3]

7.Make the biologic drugs or drug delivery systems more permeable:

To help oral delivery of biologic drugs, which are often poorly absorbed in the gastrointestinal tract (GI), researchers have investigated a number of novel methodologies [4]. In these studies, one of the approaches was to chemically modify the biologic and/or to modify it with transport-enabling (receptor-mediated transport) molecules, such as peptides or proteins, that can readily cross the intestinal epithelium through natural receptor-mediated mechanisms (e.g. by using polymeric nanoparticles) [5]. The other method showed potential innovative use of biodegradable polymeric nanoparticles as drug carriers. The polymer nanoparticles can protect biologics from degradation in harsh gastrointestinal conditions, can deliver drugs as intended from its nano size, and can also interact with specific receptors on particular intestinal epithelial (enterocyte) cells (e.g. the neonatal Fc receptor), enhancing directed delivery [6]. Preclinical studies have shown that nanoparticles that target FcRn demonstrate a more effective absorption and therapeutic response to a drug than normal absorption and therapeutic response to drugs such as exenatide and insulin [7]. Not to be discouraged, there remain major obstacles in the use of nanoparticle delivery methods for biologics such as nanoparticles limited drug loading, the low transport capacity of biological receptors, and the potential that nanoparticles will not be working compounds or may be inefficient at specific absorptive points along the intestinal track due to disintegration or interactions with intestinal fluids that block specific uptake. Thus, nanoparticle delivery systems within nanomedicine is a real possibility however these delivery systems are to translate these empirical results based in biologics [3]

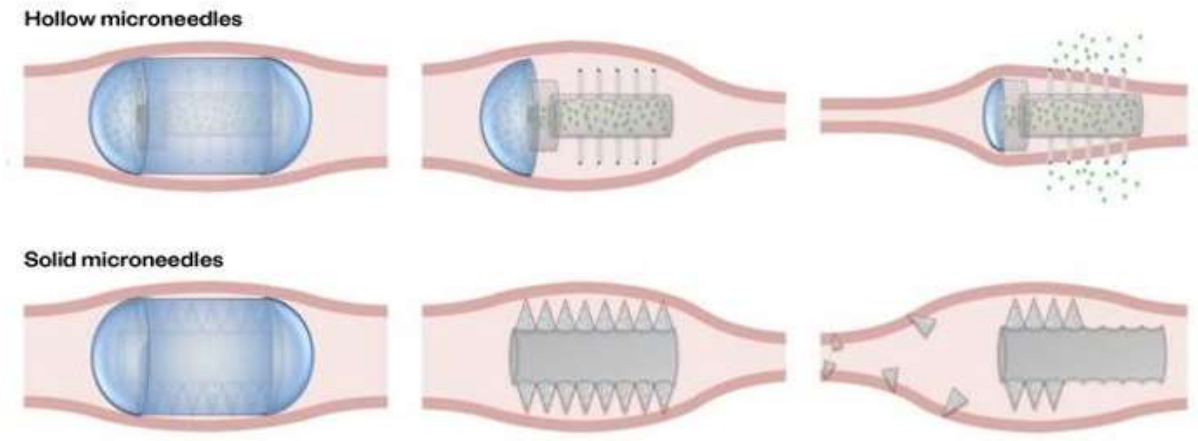

Fig. 1: Therapeutic use concept of hollow and solid microneedle pills in the gastrointestinal tract.

Advantages of oral delivery of biologics:

1.Better Patient Compliance and Convenience

2. Reduced Costs and Burden of the Healthcare System

3. Reduced Injection-Related Complications

4. Improved Quality of Life of Long-term Patients

5. Drug Concentrations May be More Stable [2,3]

Challenges Faced by Oral Delivery of Biologics:

1. Low drug-loading capacity of nanoparticle carriers
2. Poor protection from gastrointestinal degradation
3. Limited absorption due to weak interaction with intestinal fluids
4. Low permeability across the intestinal lining [4]

8.The Dose and Size of Biologics Dependency to Dictate Delivery Strategy:

Size and molecular weight of biologics are the most important factors in making effective delivery strategies non-invasive. The absorption is mostly a function of size and the dose, with increased doses tending to increase diffusion as higher concentration works as a catalyst. Even biologics of the same structure may have different absorption patterns at different doses. Moreover, every delivery site exhibits its own specific biological barriers that influence diffusion and absorption, so it is important to know site-specific characteristics while formulating delivery routes. The information is very important to make alternatives like oral or subcutaneous delivery more bioavailable. The advancements in the clinical area have also rendered high-volume subcutaneous injections more viable, which are being aided by new commercial technologies that can facilitate effective delivery of high-dose biologics.

Table no:1 Comparsion of different routes of absorption for biologics: Advantages, Disadvantages, Challenges and Delivery systems[4]

Route of Absorption	**Advantages**	**Disadvantages**	**Challenges**	**Biologic Delivery System**
Intravenous	-Rapid onset - 100% bioavailability - Large volume possible	-Painful injection - Requires healthcare setting	None	Various peptides and antibodies are approved by clinical experts
Subcutaneous	Self-administered Avoids first pass metabolism	Painful	Extra cellular Limited space of injection	Several proteins and antibodies given orally.

Route of Absorption	**Advantages**	**Disadvantages**	**Challenges**	**Biologic Delivery System**
Transdermal	Self-administered Non invasive	Transport barriers Slow absorption	Poor penetration of large molecules - Limited to superficial targets	Several vaccines that are given to human beings.
Oral	Self-administered Non invasive	Chemical environment is harsh. Easy degradation	Mucus Bacteria Gastric issues Acid Enzymes Protease Epithelial cells	Insulin as capsules given to diabetic patients.
Inhaled	Rapid absorption Large surface of absorption Non invasive	Dosing variability	Surfactant Mucus Macrophages	Inhaled insulin (Afrezza)
Buccal	Non invasive Rapid absorption Avoid first pass metabolism	Less area for absorption Irrigation is likely to occur	Mucus Epithelial cells	Insulin as buccal films.
Nasal	Easy to use - Avoids GI degradation	Less area for absorption Irrigation is likely to occur	Mucus Epithelial cells	Several vaccines. Eg: nasal spray

REFER N0[4,5]

9.Applications of Oral Biologics :

One of the emerging areas of pharmaceutical research is oral biologics, which seeks to merge the advantages of biologic treatment with the convenience of oral treatment. Biologics, including proteins, peptides, monoclonal antibodies, and nucleic acid-based drugs, have historically been delivered by injection because they are unstable within the GI tract. Advances in drug composition and delivery technology in recent years have created a variety of treatment opportunities:

1. Diabetes Management: Oral biosimilars, specifically oral insulin, is one of the most studied oral biologics, providing a less-invasive method of insulin delivery as a substitute for injectable intravenous insulin. There is a potential for less weight-gain and reduced risk of hypoglycemia while mimicking of the biological model of insulin production. In the setting of Type-2 diabetes, other peptide hormones that lower glucose (GLP-1 receptor agonists for example, oral semaglutide) are in development.[6]

2. Autoimmune Diseases: Research on oral-delivery of biologics, in the form of TNF-α inhibitors or modulators of interleukin, has been explored for ulcerative colitis, Crohn's disease and rheumatoid arthritis. Oral biologics as medications that specifically target a part of the body could potentially reduce systemic adverse effects and improve the medication's efficacy.[7]

3. Oncology: The development of oral biologic treatments specifically aimed at pathways in cancer cells or altering immune function. Oral biologic can involve DNA/RNA-based therapies, tumor-specific antibodies, and oral checkpoint inhibitors.

4.Infectious Diseases: Oral delivery of antiviral peptides, therapeutic antibodies, or nucleic acid vaccines, is being tested for the treatment or prevention of chronic infections, including HIV, hepatitis B, and even COVID-19. Oral vaccines, in particular for mucosal immunity, can be an area of innovation for effectiveness in humans[.12]

5.Enzyme Replacement Therapy (ERT): Oral biologics may also provide alternatives to ERT intravenously for genetic disorders, like Gaucher's and Fabry disease, making regimen adherence easier for patients.

6.Gastrointestinal Disorders: For SanGiovanni et al. treatment of inflammatory bowels disease (IBD) and colon cancer with biologics, it holds great promise, with biologics addressing the local inflammation (e.g., oral antibodies, cytokine blockers or even RNA therapies!).Site specific delivery systems can also protect the biologic from degradation in the stomach and delivered directly to the affected area.

7.Hormonal Disorders: Current research on oral biologics for treating various conditions of importance pertaining to hormonal disorders, for example, growth hormone deficiency, fertility and thyroid hormones. The opportunity of possible oral formulations can minimize the challenges of frequently required injections and improve personal quality of life.

8.Scaffolds for drugs and biologics delivery: A scaffold is a degradable material used in the regeneration of tissues by delivering biologics like cells, proteins, growth factors, and genes.[7]

10. Advancements in Oral Biologics:

Despite limited clinical developments in oral biologics, the increase in the use of biologics in the pharmaceutical industry has created the impetus to begin the study of this field. There are now currently a number of new and exciting approaches for drug delivery being developed as a result of many technological developments [25]. One of these approaches is prodrug design, which can improve oral bioavailability by improving GI permeability and water solubility, as well as reducing the impact created by first-pass metabolism [31]. Advances in the development of these approaches, in prodrug design, and in the area of oral biologic delivery as whole are bringing the clinical ability to effectively treat patients with biologics through oral administration even closer to a reality.

Table no: 2 Marketed formulations:(reference no 2)

S.NO	Drug Name	Disease Condition	Pharmaceutical Company
1	**Lymphocyte Modulators [27]**	**Rheumatoid Arthritis**	**Novo Nordisk A/S, Biocon Ltd**
2	**Glucagon-like Peptide 1 (GLP 1) Receptor Agonist [27]**	**Diabetes**	**Ely Lilly**
3	**Tumour Necrosis factor-alpha inhibitors [28]**	**Crohn's disease**	**Oramed Pharmaceuticals**
4	**Tofacitinib [28]**	**Irritable bowel syndrome**	**Novo Nordisk A/S, Pfizer**

11.FUTURE TRENDS:

There are many advanced techniques to enhance oral delivery of biologic drugs. Because biologic drugs are Poorly absorbed through the gut, delivering these compounds is more challenging than their oral small molecule counterparts.[29] The first general technique uses modification of the biologic chemical structure or linking it to transport-enabling molecules, such as peptides or proteins that promote transport across the intestinal epithelium via receptor-mediated transport.[23] A second approach involves utilizing biodegradable polymeric nanoparticles that carry the drug, and protect the biologic from degradation by both the stomach acid and enzymes. Biodegradable polymeric nanoparticles can also be designed to target specific receptors such as the neonatal Fc receptor (FcRn) in order to promote absorption. For example, cells have been shown to uptake FcRn-targeted polymeric nanoparticles carrying insulin or exenatide, which show improved uptake of insulin, and a longer duration for the therapeutic effect in animal studies. However, there are limitations associated with biodegradable polymeric nanoparticles including drug loading, low transport efficiency of biologic receptors, and the stability of the nanoparticles and/or competition and degradation by intestinal fluids. These limitations must be resolved to develop modern nanomedicine-based systems for the clinical use of oral delivery of biologic therapeutics.[4]

12.CONCLUSION:

Oral administration of large proteins and peptides has come a long way, with numerous clinical trials showing encouraging efficacy. Technical hurdles are being overcome, but economic and logistical considerations now present more significant challenges. The cost of biologic manufacture has fallen, and even with incomplete absorption, products with 10% biopotency are economically feasible. High proteolytic activity in the gut, previously a problem, now serves to degrade unabsorbed material and enhance safety. Attention has turned to delivery devices and excipients that are effective, safe, and inexpensive. Clinical translation is still limited because of gastrointestinal barriers and safety concerns, but increasing knowledge of GIT physiology and new material development are leading the way, making oral biologic delivery a probable clinical reality and a revolutionizing treatment for chronic diseases.

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