Recent developments in oral drug delivery of biologics

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ABSTRACT:

Oral administration of medications is typically preferred by patients because it is more convenient; however, biologics cannot currently be administered orally, due to its many advantages, such as patient compliance, non-invasiveness, and ease of drug administration, it is often the most advantageous route for physicians. Despite this, the physiological barriers of the gastrointestinal (GI) tract prevent oral biologic delivery from being effectively tested. Multiple barriers in the GI tract prevent complex macromolecules from being absorbed into the systemic circulation after consumption. Mucosal permeability, drug solubility, and environmental stability in the GI tract are some of the factors that affect how well oral medications are absorbed. The GI tract is such a harsh environment, that biologics are extremely susceptible to it. In addition to this problem, biologics comparatively high molecular sizes result in exceedingly low intestinal mucosal permeability. Oral biologics delivery research has a long and rich history and the growth of biologics in recent decades has further accelerated research activity. To improve oral drug absorption, a variety of pharmaceutical technologies and drug delivery systems, such as cyclodextrins, micelles, nano-carriers, and lipid-based carriers, have been investigated. Physiological barriers to oral biologic delivery are outlined in this article, along with various research approaches to enable or enhance oral biologic delivery. The advantages and disadvantages of oral drug delivery methods will also be highlighted, along with the general feasibility and potential of this future clinical field.

Keywords: Oral drug delivery; absorption enhancers; biologics; gastrointestinal barriers; insulin; microneedle pill;

1. INTRODUCTION:

1.1The Role of Biologics:

Biologics are medicines that affect a number of products from living organisms such as vaccines and recombinant proteins. Biologics have transformed and enhanced the therapy of numerous disorders, (e.g. inflammatory bowel disease [IBD], rheumatoid arthritis), cancer, and diabetes. Despite being in clinical use for a very long time—nearly 100 years in the case of insulin—their development and use have significantly grown over the past, because of improvements in biotechnology and increased knowledge of biology and disease processes, over the past two decades. Biologics made up eight of the top ten selling medications in 2018 (based on global sales in US dollars) [1]. Biologics differ from chemically derived pharmaceuticals and particularly with consequences relating to the administration, manufacture, associated costs, and therapeutic efficacy of other conventional medicines. Compared to small molecule drugs, biologics often have greater molecular weights and an inherent heterogeneous structure. Biologics are large, complex molecules that are particularly sensitive to the GI environment's physical and chemical characteristics, with a few exceptions, biologics are currently administered by injection because of this sensitivity [2-5].

1.2 Advantages of Oral Delivery Systems:

1. The manner in which therapy is delivered is one aspect of the patient treatment experience, compared to other parenteral routes like intravenous (iv), intramuscular (im), and subcutaneous (sc) injections, as well as an inhalation for asthma treatments, patients are typically more compliance with oral formulations.
2. Additional advantages of oral delivery over intravenous administration include: For example, oral insulin delivery more nearly resembles the physiology of pancreatic endogenous insulin secretion, which results in lower levels of systemic insulin and reduces the risk of weight gain problems and hypoglycemic episodes.
3. Insulin used orally also lowers the cost and complications associated with using needles.
4. Drugs taken orally can be targeted at certain GI tracts for treatment of pathological conditions, such as infections, inflammations, and malignancies of the stomach and colon.
5. Orally administered drugs (such as tablets, capsules, solutions, syrup, suspensions, emulsions and powders, etc.) are ingested after being placed in the mouth.
6. Due to its many advantages, including ease of administration, patient compliance, and cost-effectiveness, oral drug delivery offers a useful alternative for treating a variety of deadly diseases.
7. Current estimates indicate that oral formulations make up roughly 90% of the overall global market for pharmaceuticals intended for human use.
8. Approximately 84% of the top-selling drugs, which are currently worth $35 billion, are pharmaceuticals intended for oral administration. [6]. Drugs that are taken orally are typically the most practical for frequent and extended use. In non-sterile conditions, patients can administer their own drugs, which might increase patient compliance.

1.3 Developments in the Oral Biologics Field:

The clinical application reality has unchanged in relation to the therapeutic administration of biological medication, despite continued research in the oral delivery of biologics. However, the proliferation of biologics in the pharmaceutical market has accelerated the study of potential clinical applications [6]. The development of more clinically applicable drug delivery techniques as a result of research into oral delivery of biologics relevant to technological advancements has the potential to make oral administration of biologics an option. Some practical design alternatives, such as the prodrug design, can increase the water solubility and GI permeability of drugs to increase their oral bioavailability and overcome first-pass metabolism.

2. UPTAKE OF BIOLOGICS:

2.1 Physiological Barriers to the Oral Uptake of Biologics:

Overcoming the physiological barriers of the GI tract is one of the biggest challenges to attaining clinical oral administration of biologics. The GI tract is responsible for limiting the absorption of foreign materials from the environment, particularly harmful microorganisms or their byproducts. Another barrier to the uptake of biologics is the chemical barrier found within the GI environment. Protein breakdown into individual amino acids, dipeptides, and tripeptides is known as proteolysis, which is pH-induced is a significant chemical barrier [7]. The intestinal epithelium is the biggest and most important barrier to the absorption of biologics. Although it is only one cell thick, the arrangement of its cells creates a nearly continuous cell membrane barrier that faces the lumen. Additionally, the layer of mucus above the epithelium, which varies in thickness depending on the area of the gut, may function as a barrier to prevent the diffusion of biologics to the epithelium beneath. Basement membranes can prevent macromolecules from penetrating the region below the epithelium, hence restricting systemic absorption. They are present as thin, specialized sheets of extracellular matrix between the epithelium and connective tissue. These elements greatly influence why less than 1% of biopharmaceuticals bioavailable are oral [8]. Drugs low chemical and biological stability, as well as physiological barriers like efflux transporters, ph, and metabolic enzymes, can further affect how well they are absorbed. The human anatomy's biological barriers have an impact on how quickly biologics taken orally are absorbed. The duodenum and jejunum, which are located in the upper GI tract, are primarily responsible for absorbing the majority of orally delivered drugs. Due to its smaller surface area and thicker mucus layer than the intestine, the stomach has a lower capacity for drug absorption. One of the main GI tract barriers to drug absorption is the intestinal epithelial epithelium. The single-column layer of epithelial cells is primarily responsible for allowing hydrophilic molecules to flow through.

A small intestine cell's 3,000–7,000 microvilli offer a lot of surface area for drug interaction and absorption, but they also operate as an enzymatic barrier because the brush border is highly concentrated in digesting enzymes [9]. Drugs must pass through a number of layers in order to be absorbed from the GI tract lumen and reach the epithelium, mucosa, and blood or lymph capillary walls, including gastric juice, pericellular matrix, and mucous-rich layer.

The pH of the GI fluid is another aspect that affects drug absorption; as a result, drugs with poor stability under acidic pH need to be protected in the stomach. The bioavailability of oral biologics can also be impacted by the GI tract's active movement and contraction. The transit rate and thus, the residence time of a drug following oral administration are principally determined by the peristalsis motilities. Drugs may travel the mucous membranes of GI organs such as the mouth, esophagus, stomach, duodenum, jejunum, ileum, and colon as they move along the GI tract. They are removed in the feces and are not fully absorbed by the intestine if they are unable to pass the membranes by the time they reach the colon.

Food can decrease, increase or otherwise affect how quickly drugs are absorbed. Food has an impact on GI processes like gastric emptying, bile acid secretion, intestinal transit time, pH change in the stomach, and increased blood flow to the liver. Additionally, it can change a drug's solubility, size, intestinal permeability, and dissolution profile, among other physicochemical properties. In general, the food taken at the time of administration can have an impact on hydrophobic drugs or drugs whose solubility is pH-dependent. Drug metabolism can affect their oral bioavailability in addition to their solubility and permeability.

2.1.1 Physiological barriers to biologics absorption in the intestine:

Several physiological barriers, such as stomach acid and enzymes, hinder the systemic absorption of biologics after oral delivery. Additionally, the mucus prevents macromolecules from diffusing freely [10]. Typically, hydrophilic macromolecules cannot penetrate the intestinal epithelium. Additional impediments to the intestinal absorption of biologics may include the capillary endothelium and the basement membrane made of extracellular matrix

3. STRATEGIES FOR ENHANCING ORAL BIOLOGIC DRUG DELIVERY:

3.1 Protect the biologic from acid and enzymatic degradation:

Reducing acid degradation is one method that can improve the bioavailability of biological drugs. This can be achieved by taking the medication orally and coating it with a polymer barrier or enteric coating that prevents it from dissolving or integrating into the stomach. Biotherapeutics can be protected from proteolytic enzymes in the intestinal environment by protease inhibitors when protein and peptide medications are co-administered with them. Some biologics, especially peptides, can also have their chemical structures changed in order to increase their stability in GI fluids [11]. Any methods that aim to enhance the oral delivery of biologics must ensure that the biological medication is protected against acid and enzymatic degradation. The benefits of dosage formulations with prolonged gastric residence periods are greatest for medications that are absorbed largely in the stomach or upper GI tract or that have solubility problems in the intestinal fluid [12]. The advantage of this strategy covers controlled or sustained oral administration as well can reduce fluctuations in systemic drug concentration as well as increase patient compliance by lowering the dose of drugs administered to patients who needs the number of dosages.

3.2 Increase the biologic's time in contact with the absorbent epithelium:

Given the length of the intestines and the fact that the medication is currently in close proximity to the absorptive epithelium and has a high concentration, the goal of this method is to prevent luminal loss of the drug. Typically, mucoadhesive materials are polymers that can interact with mucus through ionic and non-ionic interactions, this can help prolong absorption by extending the time that the medication spends at the absorption site [13]. Chitosan, gelatin, pectin, guar gum, sodium alginate, and xanthan gum are examples of natural mucoadhesive polymers [14]. While cellulose derivate, poly acrylic acid, polyethylene glycol, polyethylene oxide, polyvinyl pyrrolidone, and polyvinyl alcohol are examples of synthetic mucoadhesive polymers [15], with varied success, many of these materials have been looked into for oral biologic drug delivery [16]. Salmon calcitonin (sCT), a therapeutic polypeptide, can be delivered orally more effectively via a mucoadhesive "transdermal patch-like" system [17]. It was supplied in gastro-resistant hard gelatin capsules and was based on mucoadhesive polymers (pectin, sodium carboxymethylcellulose, and carbopol 934). *In vivo*, the method significantly improved intestinal sCT absorption, similar mucoadhesive patches for oral delivery of exenatide and insulin have been studied by Gupta et al [18]. Blood glucose decreased by 42% when these systems were surgically implanted in the rat jejunum, but not in the insulin solution-treated group (the control). Compared to intestinal injections, the relative bioavailability of insulin and exenatide significantly increased (13-fold and 80-fold, respectively). Although mucoadhesive systems have shown promise for oral biologic administration *in vitro* and *in vivo*, this approach may face challenges such as low efficacy, especially with larger biologics (e.g. monoclonal antibodies). It might not be enough to simply increase the biotherapeutic's residence duration at the absorptive surface to achieve bioavailability in a clinically significant way. Given the restricted ability of hydrophilic drugs with molecular weight orders of magnitude exceeding 500 Da to get through the intestinal epithelium, this is understandable.

3.3 Increase the Permeability of the Biologic Drug:

A chemical change to a molecule to give its epithelial-permeating qualities is another way to increase the oral bioavailability of biologics. It is also feasible to improve the biotherapeutic's capacity to penetrate the intestinal epithelium by coupling it to another molecule with similar abilities. The "transport-enabling molecule" may be joined chemically or by biotechnology-mediated fusion techniques [19]. Other peptides or proteins that use biological transport routes to traverse the epithelium are examples of transport-enabling molecules. Based on this, biologic carriers can have several advantages over biodegradable polymeric nanoparticles. For example, certain nanoparticles provide the safety of the therapeutic drug from GI tract acid and enzymes [20].

For the oral delivery of biologics, nanoparticle-based drug carriers are designed with certain substances that function as ligands for biological transport receptors. Many research teams have looked into these delivery techniques, including nanoparticles that exploit the G-immunoglobulin, vitamin B12, and intestinal epithelial transport mechanisms. When compared to the intestinal epithelium, these systems considerably and quickly transported unaltered nanoparticles [21].

One of the most important aspects of biological membrane permeability is drug distribution and absorption. There may be poor permeability due to a variety of structural characteristics and membrane-based pathways for efflux [22]. Membrane permeability frequently limits the distribution and transfer of pharmaceuticals after they have been delivered to the tissue. Although these substances are useful pharmacologically. Low permeability causes poor absorption, which becomes the rate-limiting factor to achieve acceptable bioavailability.

3.4 Using "smart" ingestible devices, overcome the mucosal barrier:

Ingestible "smart" technologies, such as ultrasonic and microneedles, can be utilized to improve the intestinal absorption of biologics in addition to protecting the therapeutic from the unfavorable GI environment[23]. The capsule intended to stay in place is used in microneedle technology intact in the stomach, then injects itself into the small intestine, the intestinal wall with the medication. This procedure is painless, due to the gut mucosa's lack of pain receptors and has demonstrated impressively equivalent to or better insulin bioavailability to subcutaneous injections. This approach has the advantage of enabling the administration of biologics with low to medium molecular weights, and it may also be able to deliver biologics like antibodies in higher doses [24].

To prevent disintegration, the capsules encasing the microneedles can be coated with a pH-responsive substance. Transmitting using the coating might disintegrate and release the ligand from the receptor cells' microneedles, for systems utilizing hollow microneedles through peristalsis the drug reservoir is compressed, releasing the drug through the needles. For systems that use solid microneedles, the drug is formulated for the microneedles that penetrate the tissue and break free from the pills and fragments, allowing the needle to release the according to the formulation of the needle, drug in a controlled manner. After the microneedles are stuck in the GI tissue after drug release until biodegradation.

The "self-orienting millimeter-scale applicator" (SOMA), another recent technical innovation, can alter the physical composition of the drug used to deliver a biologic through a biodegradable needle [25]. In this oral health system, a similar form and low center of gravity are utilized in biologic delivery for gravity to self-orientate in a correct position. Physically insert a biodegradable microneedle through the membrane of the stomach bio therapeutics administered throughout the body.

4. FUTURE TRENDS:

One of the most popular drug delivery methods is the oral route administered to patients who are both adults and children. Conventional Oral formulations may cause complications and problems that could be resolved via sophisticated formulation techniques. Significantly the future, the factor that still needs further thought is the development of reliable *in-vitro*, *in-vivo* correlation models that enhanced *in-vivo* performance and data generation and provide cost-benefit over existing formulations[26]. This will assist speed the shift to more relevant and realistic formulations from the laboratory to large-scale industrial manufacturing. When designing new formulations, the intended patient population must also be taken into account. By employing

already available nanoparticle technology to create therapeutic formulations for adults, future research can aim to build improved pediatric formulations.

To move a lead molecule from drug discovery to clinical trials, the overall period for formulation development is anticipated to be shorter than the current one. Pharmaceutical researchers will, however, have to overcome a number of challenges to develop better and more potent oral formulations that can improve therapy.

5. MARKETED FORMULATIONS:

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

6. CONCLUSION:

Devices for oral biologic drug delivery systems are showing substantial promise for development in medical advancement, yet, there hasn't been much research done in this area. While every drug delivery method mentioned has demonstrated they have achieved notable outcomes in conceivable pharmacokinetic scenarios, still needs to be clinically proven effective by patients.

A safer option might be one that relies on improving utilizing biological transport to increase biologic absorption in the intestine methods to administer without causing tissue damage. However, these are likely to encounter capacity issues and may be more appropriate for stronger biologics. Furthermore, although the costs of these technologies are not yet known, they probably in the short-to-medium term to be high, in which case it is important to take into account the biologic, illness area, and patient population for making advantage of various drug delivery methods.

There has been significant progress in the study of biologics oral administration. Progress, but hasn't produced a significant impact in the clinic to date. The lack of clinical translation in this field reflects in part the extremely strong physiological barriers in the GI tract, which have typically been connected to the safety of drug delivery strategies. However, a greater understanding of the physiological barriers and the recently unprecedented. Advances in this field are being driven by materials and are probably going to make oral biologic drug delivery a clinical reality.

REFERENCES:

[1]. Urquhart L. Top drugs and companies by sales in 2018. Nat Rev Drug Discov 2019;18(245). doi: 10.1038/d41573-019-00049-0

[2]. Eek D, Krohe M, Mazar I et al. Patient-reported preferences for oral versus intravenous administration for the treatment of cancer: a review of the literature. Patient Prefer Adherence 2016;10:1609–1621. doi: 10.2147/ppa.s106629

[3]. Pridgen EM, Alexis F & Farokhzad OC. Polymeric nanoparticle drug delivery technologies for oral delivery applications. Expert Opin Drug Deliv 2015;12(9):1459–1473. doi: 10.1517/17425247.2015.1018175

[4]. Sosnik A & Augustine R. Challenges in oral drug delivery of antiretrovirals and the innovative strategies to overcome them. Adv Drug Deliv Rev 2016;103:105–120. doi: 10.1016/j.addr.2015.12.022

[5]. García-Pérez LE, Alvarez M, Dilla T et al. Adherence to therapies in patients with type 2 diabetes. Diabetes Ther 2013;4(2):175–194. doi: 10.1007/s13300-013-0034-y.

[6]. Urquhart L. Top drugs and companies by sales in 2018. Nat Rev Drug Discov. 2019; 18: 245.

[7]. Khanvilkar K, Donovan MD & Flanagan DR. Drug transfer through mucus. Adv Drug Deliv Rev 2001;48(2–3):173–193. doi: 10.1016/s0169-409x(01)00115-6.

[8]. Khanvilkar K, Donovan MD, Flanagan DR. Drug transfer through mucus. Adv Drug Deliv Rev. 2001; 48: 173-193.

[9]. Homayun B, Lin X, Choi HJ. Challenges and recent progress in oral drug delivery systems for biopharmaceuticals. Pharmaceutics. 2019; 11: 129.

[10].Original submitted: 26 April 2019; Revised submitted: 20 June 2019; Accepted for publication: 6 September 2019; Published online: 10 January 2020; doi: 10.1211/PJ.2020.20207374

[11]. Crowe JS, Roberts KJ, Carlton TM, et al. Preclinical development of a novel, orally-administered anti-tumour necrosis factor domain antibody for the treatment of inflammatory bowel disease. Sci Rep. 2018; 8: 4941

[12]. Andreas Bernkop-Schnürch. Mucoadhesive systems in oral drug delivery. Drug Discov Today Technol. 2005; 2: 83-87.

[13]. Bernkop-Schnürch A. Mucoadhesive systems in oral drug delivery. Drug Discov Today Technol 2005;2(1):83–87. doi: 10.1016/j.ddtec.2005.05.001

[14]. Cook SL, Bull SP, Methven L et al. Mucoadhesion: a food perspective. Food Hydrocolloids 2017;72:281–296. doi: 10.1016/j.foodhyd.2017.05.043

[15]. Rossi S, Vigani B, Sandri G et al. Recent advances in the mucus-interacting approach for vaginal drug delivery: from mucoadhesive to mucus-penetrating nanoparticles. Expert Opin Drug Deliv 2019;16(8): 777–781. doi: 10.1080/17425247.2019.1645117

[16]. Homayun B, Lin X & Choi HJ. Challenges and recent progress in oral drug delivery systems for biopharmaceuticals. Pharmaceutics 2019;11(3):129. doi: 10.3390/pharmaceutics11030129
[17]. Gupta V, Hwang BH, Lee J et al. Mucoadhesive intestinal devices for oral delivery of salmon calcitonin. J Control Release 2013;172(3):753–762. doi: 10.1016/j.jconrel.2013.09.004
[18]. Gupta V, Hwang BH, Doshi N et al. Delivery of exenatide and insulin using mucoadhesive intestinal devices. Ann Biomed Eng 2016;44(6):1993–2007. doi: 10.1007/s10439-016-1558-x.
[19]. Sosnik A, Augustine R. Challenges in oral drug delivery of antiretrovirals and the innovative strategies to overcome them. Adv Drug Deliv Rev. 2016; 103: 105-120.
[20]. Shen S, Wu Y, Liu Y, et al. High drug-loading nanomedicines: progress, current status, and prospects. Int J Nanomedicine. 2017; 12: 4085-4109.
[21]. Rossi S, Vigani B, Sandri G, et al. Recent advances in the mucus-interacting approach for vaginal drug delivery: from mucoadhesive to mucus-penetrating nanoparticles. Expert Opin Drug Deliv. 2019; 16: 777-781.
[22].Dahlgren D, Lennernäs H. Intestinal permeability and drug absorption: predictive experimental, computational and in vivo approaches. Pharmaceutics. 2019; 11: 411.
[23].https://www.biospace.com/article/releases/first-human-studyof-and-quot-robotic-and-quot-ranipill-capsule-to-replaceinjections-announced-by-rani-therapeutics.
[24]. BioSpace. First human study of "robotic" RaniPill capsule to replace injections announced by Rani Therapeutics. 2019. Available at: https://www.biospace. com/article/releases/first-human-study-of-and-quot-robotic-and-quotranipill-capsule-to-replace-injections-announced-by-rani-therapeutics/ (accessed January 2020).
[25].Abramson A, Caffarel-Salvador E, Khang M, et al. An ingestible self-orienting system for oral delivery of macromolecules. Science. 2019; 363: 611-615.
[26.] Shen S, Wu Y, Liu Y, et al. High drug-loading nanomedicines: progress, current status, and prospects. Int J Nanomedicine. 2017; 12: 4085-4109.
[27]. https://www.coherentmarketinsights.com/market-insight/oral-biologics-market-989
[28]. https://www.researchandmarkets.com/r/46wwv4.