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COMPREHENSIVE REVIEW ON ORAL BIOLOGICS

Pravin Kumar Darji[1]*, Jayendra Kumar Patel[2], Binit Patel[3], Shalin Parikh[4] and Praneeth Ivan Joel Fnu[5]

[1,2,5]Exemplify Biopharma Inc., Cranbury, New Jersey, USA – 08512.

[3]Hovione Pharmaceutical Company, East Windsor, New Jersey, USA-08520.

[4]Shree SK Patel College of Pharmaceutical Education and Research, Ganpat University, Mehsana, Gujarat, India-384012.

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***Corresponding Author**
Pravin Kumar Darji
Exemplify Biopharma Inc.,
Cranbury, New Jersey, USA
– 08512.

ABSTRACT

Patients usually choose to take medicines orally due to its convenience. Currently, oral administration of biologics is not possible. The gastrointestinal tract performs various activities in the body, which provide challenges for the absorption of complex macromolecules ingested into the body. Biologics are highly susceptible to the harsh conditions of the digestive system and face significant barriers in traversing the intestinal mucosa. Currently, biologics provide significant promise in the treatment of metabolic illnesses, aging, and inflammatory disorders. Administering these medications orally has long been recognized as a crucial objective for chronic disorders. Despite extensive research conducted over numerous years, the administration of biologics through oral means is only now beginning to demonstrate its feasibility. There has been significant discussion over the challenges associated with the administration of biologics. An important function of the intestine is to prevent the passage of undesirable substances through it. Nevertheless, on a daily basis, various quantities of biological agents, ranging from macroscopic to microscopic, traverse the intestinal cell membrane. This paper initially discusses the primary physiological challenges associated with administering biologics orally, as well as several research strategies aimed at improving or enabling oral delivery of biologics. Additionally, it explores the normal functioning of the gastrointestinal tract. Subsequently, the document enumerates the primary biological mechanisms that have been effectively employed thus far to accomplish oral absorption, along by a thorough examination of the advantages and

disadvantages associated with each approach. The text provides many instances of distinct biologics employed, along with pertinent information regarding the outcomes of recent clinical studies. Additionally, it explores the potential applications of these biologics in real-world scenarios and speculates on the future prospects of this sector.

KEYWORD: Oral delivery, biologics, absorption enhancers, gastrointestinal barriers, insulin, microneedle pill, intestine, receptor-mediated uptake, paracellular transport, transcellular transport.

INTRODUCTION[1,19]

Biologics — medicines that include products from living organisms, like recombinant proteins, peptides, and vaccines, have changed the way many diseases are treated, including cancer, rheumatoid arthritis, and inflammatory bowel disease (IBD). They have been used in medicine for a long time—almost 100 years in the case of insulin—but their creation and use have grown a lot in the last twenty years. This is because of progress in biotechnology and a better understanding of how biology and disease work. It was found that seven of the ten best-selling drugs in the world in 2023 were biologics.

Biologics are not the same as "conventional" drugs made from chemicals in a lot of ways that affect how they are made, how they are given, how well they work in the body, and how much they cost. Small-molecule drugs, like aspirin, have a much lower molecular weight than biotherapeutics. They also have a structure that is naturally not uniform. Because biologics are made up of large, complicated molecules, they are very sensitive to the physical and chemical conditions in the gut (GI) tract. Because of this sensitivity, biologics are mostly given by injection at this point.

On the other hand, oral administration is the most convenient and preferred method of drug administration. If you take insulin by oral instead of injecting it, it has some extra benefits. For example, insulin taken by oral works more like insulin produced by your pancreas, which lowers insulin levels in your body and reduces the risk of hypoglycemia and weight gain problems. In addition, oral administration of insulin also reduces cost and needle-related complications.

This review specifically examines the intestine as the location where activity and absorption occur. Administration through the "oral route" is understood as the process of ingesting

something, which then travels through the esophagus and stomach before reaching the intestinal tract, where it exerts its effects. The process of traversing the stomach can be easily accomplished by employing pharmaceutical coatings, known as 'enteric coatings'. These coatings consist of polymer films that are applied to the exterior of a capsule, tablet, or pellet. They are designed to resist breakdown when exposed to the acidic environment of the stomach, but dissolve when they encounter the higher pH environment of the intestinal lumen. Companies such as Capsugel, ACG, and Gelita have recently developed capsules that possess these qualities without the need for coatings. It is noteworthy that humans have a greater ability to protect themselves against stomach acidity compared to animals. This is because the difference between the acidity levels in the stomach (ranging from 1 to 3) and the acidity levels in the intestines (5 and above) is larger in humans than in other mammals, including primates. In normal situations, the stomach pH of these mammals often reaches 5 or higher.

PHYSIOLOGICAL BARRIERS TO ORAL DELIVERY OF BIOLOGICS[1,19]

An important obstacle to successfully delivering biologics through the oral is overcoming the various natural barriers in the gastrointestinal tract (GIT). These barriers are specifically designed to prevent the absorption of foreign substances, such as harmful pathogens or their byproducts, from the external environment.

One significant obstacle is the breakdown of proteins into individual amino acids, dipeptides, and tripeptides due to changes in pH. The biochemical barriers consist of proteolytic enzymes present in the gut lumen (such as pepsin, trypsin, and chymotrypsin), proteolytic enzymes located at the brush border membrane (known as endopeptidases), and an efflux pump. P-glycoprotein.

Upon oral ingestion, the uptake of biologics into the bloodstream is restricted by many physiological obstacles, such as gastric acid and enzymes (not depicted). In addition, mucus impedes the dispersion of large molecules. Hydrophilic macromolecules typically cannot pass through the intestinal epithelium. The presence of the extracellular matrix-based basement membrane and capillary endothelium can create additional obstacles for the absorption of biologics in the intestines.

However, the primary obstacle that significantly hinders the uptake of biologics is the intestinal epithelium. The cells of this structure are organized in a manner that creates a

nearly unbroken cell membrane barrier facing the lumen, despite being just one cell layer thick. In addition, the mucus layer, which has different thicknesses in different parts of the digestive tract, can also function as a barrier, impeding the movement of biologics towards the underlying epithelium. Basement membranes, positioned as delicate and specialized sheets of extracellular matrix between the epithelia and connective tissue, might impede the infiltration of macromolecules into the area beneath the epithelium, hence restricting systemic absorption. These variables greatly contribute to the oral bioavailability of biopharmaceuticals being less than 1%.

STRATEGIES FOR ENHANCING ORAL DELIVERY OF BIOLOGICS[1,19]

Protect the biologic from acid and enzymatic degradation

A method that can increase the bioavailability of biologic medications is minimizing acid degradation. Delivery within enteric-coated systems, which are widely used in clinical practice, can accomplish this.

Concomitant administration of protein and peptide medications alongside protease inhibitors can shield biotherapeutics from the proteolytic enzymes found in the gut environment. It is feasible to alter the chemical compositions of certain biologics, specifically peptides, to enhance their stability in gastrointestinal fluids.

Certain biologics exhibit greater inherent physicochemical stability against enzymatic breakdown in the gastrointestinal tract (GIT) and may have the potential for oral administration. Examples encompass antibody fragments generated from sharks and llamas, with particular focus on the latter for their potential use as oral delivery anti-tumour necrosis factor-alpha biologics in the treatment of inflammatory bowel disease (IBD).

It is vital to emphasize that safeguarding the biologic medicine against acid and enzymatic degradation is a crucial necessity. Therefore, any approaches aimed at enhancing the oral administration of biologics, as described below, must also fulfill this criterion.

Increase the contact time of the biologic with the absorptive epithelium

The objective of this method is to hinder the loss of the drug within the intestines and deliver it in concentrated form to the absorptive epithelium, considering the length of the intestines.

Mucoadhesive materials are generally polymers that can interact with mucus through both ionic and non-ionic interactions. These interactions can extend the amount of time that

medicine stays at the absorption site, resulting in improved absorption. Natural mucoadhesive polymers encompass chitosan, pectin, gelatine, sodium alginate, guar gum, and xanthan gum. On the other hand, synthetic mucoadhesive polymers consist of cellulose derivatives, poly(acrylic acid) polymers, poly(ethylene glycol), poly(ethylene oxide), poly(vinyl pyrrolidone), and poly(vinyl alcohol). Several of these materials have been examined for the purpose of administering biologics orally, yielding diverse outcomes.

The mucoadhesive 'transdermal patch-like' approach enhances the oral administration of the therapeutic polypeptide, salmon calcitonin (sCT), by utilizing mucoadhesive polymers - carbopol 934, pectin, and sodium carboxymethylcellulose - delivered through gastro-resistant hard gelatin capsules. This technique has shown a substantial improvement in the absorption of intestinal sCT in living organisms. Gupta et al. have examined analogous mucoadhesive patches for the oral administration of exenatide and insulin. Implantation of these devices in the rat jejunum led to a 42% reduction in blood glucose levels, whereas the control group treated with insulin solution did not exhibit any such impact. The relative bioavailability of insulin and exenatide exhibited a significant increase as compared to intestinal injections, with a 13-fold and 80-fold increase, respectively.

Although mucoadhesive systems have shown promise in facilitating the oral administration of biologics in laboratory and live animal experiments, there are certain obstacles that need to be addressed. One of the main issues is the limited effectiveness, especially when dealing with bigger biologics such as monoclonal antibodies. Mere extension of the duration that the biotherapeutic remains at the absorptive surface may not be enough to generate a meaningful enhancement of bioavailability in clinical terms. This may be comprehended due to the restricted capacity of hydrophilic medicines, which have a molecular weight significantly above 500 Daltons, to pass through the intestinal epithelium. The impact of intestinal mucus turnover on the functioning of these systems is uncertain. Moreover, there could be possible challenges in implementing such systems in disorders linked to mucus abnormalities, such as Inflammatory Bowel Disease (IBD).

Make the mucosal barrier more permeable

The following tactics are frequently studied to enhance the oral bioavailability of biologics, as they can modify both the intestinal mucus barrier and the epithelial barrier.

Enhancing the permeability of the mucus barrier can be achieved by employing mucolytic drugs, such as N-acetylcysteine, which have the ability to break down mucus. This can lead to an improvement in the dispersion of large molecule biologics. Nevertheless, as the epithelium is normally the primary limiting factor, rather than the mucus, it is generally more beneficial to modify the former. Chemical absorption enhancers, such as surfactants and other substances, can modify the epithelial barrier by opening tight junctions in the epithelium.

SURFACTANTS[1,19]

These substances possess both a water-attracting and water-repelling component, allowing them to adhere to the boundaries of a system and modify the energy and tension at these boundaries. This leads to the fluidization of the plasma membrane of the intestinal epithelium, as well as the temporary opening of tight junctions in the epithelium, so enabling the passage of large molecules.

The primary contenders being employed in the advancement of oral peptide formulations are surfactants derived from medium-chain fatty acids (such as sodium caprate, sodium caprylate, and N-[8-(2-hydroxybenzoyl)amino]caprylate [SNAC]), bile salts, and acylcarnitines. Current clinical trials are evaluating technologies like as the 'gastro-intestinal permeating technology' and the 'eligen' technology, both developed by Novo Nordisk, which make use of these materials. A recent report indicated that a formulation of SNAC was used to orally administer semaglutide, a long-acting GLP-1 analogue developed by Novo Nordisk, for the treatment of type 2 diabetes mellitus. This formulation successfully completed the first phase IIIa trial. The trial, consisting of 703 participants, successfully met its main goal by showing significant enhancements in HbA1c levels for three different dosages of orally-administered semaglutide (3mg, 7mg, and 14mg) as compared to a placebo. Furthermore, high-dose SNAC-containing vitamin B12 tablets are currently available in the market.

The efficacy of Mycapssa (Chiasma) capsules is currently being evaluated in three worldwide phase III trials, showing promising prospects. Chiasma, an Israeli biopharmaceutical business, created the 'transient permeability enhancer' (TPE) technology that is currently employed in the Mycapssa capsule formulations. These capsules are used for the maintenance therapy of adult patients with acromegaly. The active ingredient in this formulation is the peptide octreotide, which is an analogue of somatostatin. The utilization of TPE technology can increase the oral bioavailability of octreotide due to the synergistic effect of

pharmaceutical excipients. This combination forms an emulsion of hydrophilic particles in a hydrophobic matrix.

Octreotide, along with sodium caprylate and other additives, is dissolved in the hydrophilic component. The surfactants used in this formulation induce the transient widening of tight junctions, enabling the medication, which is shielded from digestive enzymes, to penetrate the intestinal epithelial membrane and enter the circulation.

TIGHT JUNCTION-OPENING PERMEATION ENHANCERS[22]

Numerous substances with the ability to disrupt epithelial tight junctions, such as surfactants, have been discovered through extensive study conducted over several decades. Epithelial tight junction-opening is a promising strategy to enhance the permeability of the intestinal epithelium. This allows the medicine to bypass the epithelial cells and instead be absorbed in a cytoplasmic milieu that is rich in enzymes.

The procedure entails expanding the gap between neighboring epithelial cells (known as the paracellular space), which is typically too narrow to contain biologics. Nevertheless, it is crucial for tight junction-opening to be reversible in order to preserve the epithelium's physiological function as a secure barrier. Chitosans are the chemicals that have been extensively studied for their ability to reversibly open epithelial tight junctions, however there are other materials that have also demonstrated this property. These substances are obtained from the organic compound chitin, which is present in the cellular structures of fungi and the outer coverings of arthropods, including crustaceans and insects. Multiple iterations of chitosans have been examined; yet, similar to other substances that promote permeation, the lasting consequences of repeatedly opening tight junctions in the intestinal epithelium remain uncertain and necessitate additional investigation.

It is important to acknowledge that drug delivery methods that utilize chemicals to alter the mucosal barrier, namely absorption enhancers like surfactants and tight junction-opening agents, depend on the concentration-dependent impact on the permeability of the barrier. Hence, the clinical significance of this approach may pertain to the possible variations in absorption due to fasting or eating, as well as the amount of water used when swallowing solid medications. Furthermore, the lasting consequences of repeatedly changing the permeability of the gastrointestinal tract (GIT) are currently uncertain and necessitate thorough assessment.

Make the biologic drug or drug delivery system more permeable

By employing chemical modification, it is feasible to modify the structure of the biologic in order to enhance its ability to permeate epithelial barriers. Additionally, it is feasible to enhance the biotherapeutic's capacity to traverse the intestinal epithelium by conjugating it with another molecule that possesses this capability. Usually, this substance that facilitates transportation moves through the layer of cells lining the intestines by binding to a particular receptor found in those cells. The two entities can be linked together either by chemical conjugation or through fusion technologies facilitated by biotechnology. Transport-enabling molecules encompass peptides or proteins that exploit biological transport mechanisms to traverse the epithelium.

Researchers have not only modified the biologic to enhance its ability to pass the intestinal barrier, but they have also integrated biotherapeutics into drug carrier systems capable of traversing the intestinal barrier. Biological carriers used for this purpose are usually in the nanometer range and are made of biodegradable polymeric nanoparticles, which offer several benefits. For instance, several nanoparticles provide safeguarding for the medicinal medicine against the acidic environment and enzymes found in the gastrointestinal tract (GIT). Furthermore, the precise administration of drugs can be accomplished by targeting specific receptors present on the outer layer of intestinal epithelial cells. Similarly to large molecule biologics, nanoparticle carriers are generally not efficiently absorbed by the intestinal mucosa. Nanoparticles have limited diffusion within the intestinal mucus and lack the ability to traverse the intestinal epithelium. Nanoparticle-based drug carriers for oral delivery of biologics are designed with unique surface materials that function as ligands for biological transport receptors found in intestinal epithelial cells. Various research groups have investigated delivery strategies, such as nanoparticles that utilize the intestinal epithelial transport channels of immunoglobulin G (IgG) and vitamin B12.

Although nanomedicine-based solutions show promise and offer prospective benefits during preclinical research, their advancement is hindered by various challenges:

1. Nanoparticle carriers may have limited capacity to hold therapeutic substances, especially larger biologics like monoclonal antibodies.
2. The ability of these systems to deliver substances may be hindered by the low transport capacity of the biological pathways they utilize.

3. The intricate nanocarriers may experience significant degradation or modification in the gastrointestinal tract, particularly in the presence of highly complex intestinal biofluid. The primary concern lies in the attachment or adsorption of substances that are often found in the intestinal biofluid, such as peptides and proteins, onto the surface of nanocarriers. This interaction affects the nanocarriers' capacity to effectively target biological receptors and utilize these systems for transporting substances across the epithelial barrier.

Overcome the mucosal barrier using smart ingestible devices

Furthermore, ingestible 'smart' devices not only shield therapeutic substances from the adverse conditions of the gastrointestinal tract (GIT), but also improve the absorption of biologics in the intestines using various methods such as ultrasound and microneedles. Rani Therapeutics, a business based in the United States, is currently developing the microneedle oral delivery technology. According to the company, the ongoing preclinical research has yielded promising outcomes.

The technology utilizes a specially engineered capsule that remains intact within the stomach. Once it reaches the small intestine, the capsule administers the drug by injecting it into the wall of the intestine (see to Figure 1). The absence of pain receptors in the intestinal mucosa makes this method painless. Furthermore, it has demonstrated remarkable insulin bioavailability, which is comparable to or even superior than subcutaneous injections. This method offers the benefit of delivering not only low-to-medium molecular weight biologics but also bigger biologics, including antibodies.

The capsules are originally covered with a pH-responsive coating to facilitate swallowing. Once the tablet has reached the intended place in the gastrointestinal tract (GIT), the coating disintegrates, thereby releasing the microneedles. In systems including hollow microneedles, the drug reservoir undergoes compression by peristalsis, resulting in the release of the drug through the needles. In systems employing solid microneedles, the medicine is incorporated into the microneedles themselves. These microneedles pierce the tissue and detach from the pill, allowing the needle to gradually release the drug in a regulated manner, determined by the composition of the needle. Following the release of the medicine, the microneedles remain firmly embedded in the gastrointestinal tissue until they undergo biodegradation.

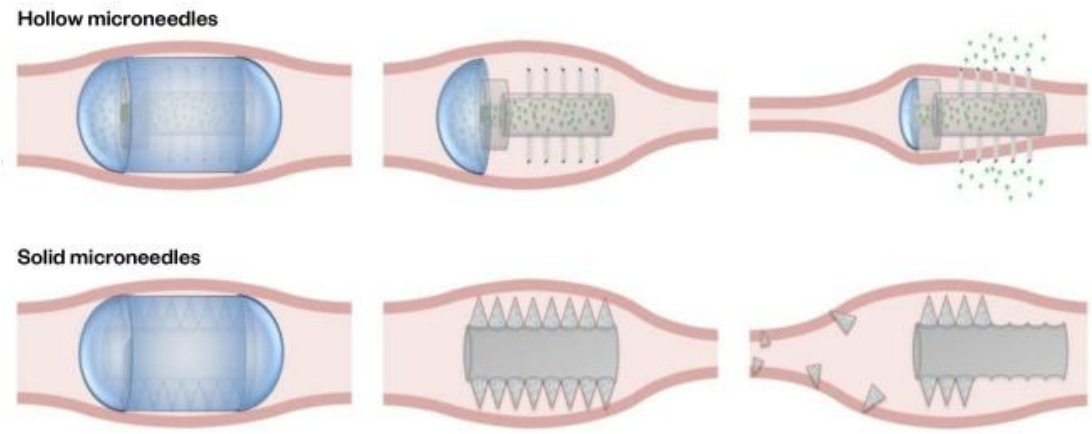

Fig. 1: Therapeutic use concept of hollow and solid microneedle pills in the gastrointestinal tract.

Potential for clinical translation of oral biologics delivery strategies

Oral delivery devices for biologics are displaying considerable promise, while research in this field is still in its early stages. Although several medication delivery techniques mentioned earlier have demonstrated promising outcomes and potential in both in vivo and in vitro settings, their application in patients has not been implemented yet. Regrettably, the administration methods mentioned before frequently prioritize either safety or efficacy, making it improbable for these tactics to advance to the clinical stage. Moreover, it is widely recognized that the permeation enhancers utilized in current oral peptide clinical trials are responsible for causing harm to the epithelial lining of the small intestine. While tissue damage is typically transient and fixable, it is uncertain if persistent administration of these absorption enhancers could override the body's repair systems.

An alternate approach that could enhance the intestinal absorption of biologics by utilizing biological transport systems to achieve delivery without causing tissue damage may offer increased safety. However, it is important to note that these methods may have limited capacity and may be most effective for highly potent biologics. These gadgets must convincingly prove their safety when used multiple times in humans; it appears that their effectiveness is not a concern. Moreover, the expenses associated with these technologies are now uncertain, but are expected to be substantial in the near-to-mid-term. Therefore, it is crucial to meticulously evaluate the choice of the biologic, disease area, and patient group for the implementation of these drug delivery systems.

RECEPTOR-SPECIFIC APPROACHES—BIOLOGICAL METHODS OF ENTRY[22,86]

This method involves harnessing the body's systems that facilitate the movement of certain molecules over the intestinal wall, but instead using them to transport a targeted therapeutic payload.

Vitamin B12/Intrinsic Factor

This serves as the quintessential model for the transportation of macromolecules across the gut through receptor-mediated mechanisms. In this case, enterocytes internalize intrinsic factor, a sizable protein. Therefore, the only requirement is to affix another protein to Vitamin B12, which already binds to intrinsic factor. All other components of the transcellular pathway should already be present.

In the duodenum, intrinsic factor (IF) attaches to Vitamin B12 (also called cobalamin) and carries it to a receptor called cubilin on the membrane of epithelial cells in the ileum. Intrinsic factor is a protein with a molecular weight of around 60 kilodaltons. It is composed of alpha and beta domains that are connected by a flexible linker. IF forms a complex with cobalamin by sandwiching the vitamin between its two domains, resulting in the creation of a novel epitope that is recognized by cubilin. The mutated IF is internalized within the cell by its binding to cubilin, along with the membrane protein amnionless. Cobalamin possesses a greater quantity of functional groups that can be utilized for the conjugation of medicines and proteins. Although most of these components are concealed when the vitamin is trapped within the crevice between the alpha and beta domains, certain sections of the molecule remain visible in the IF/cobalamin complex. One notable exposed area is the nucleoside hydroxyl group, which allows for the attachment of biologics without disrupting the binding of cobalamin to IF or the binding of the IF/cobalamin complex to cubilin, and subsequent internalization. After being transported into the lysosomal vacuole, the intrinsic factor (IF) is broken down by cathepsin L, a cysteine protease that specifically targets aromatic residues. The degraded IF is then transferred to transcobalamin (TCII), which facilitates its exocytosis. Fortunately, the cobalamin has a binding mechanism to TCII that closely resembles that of IF. This allows agents to be linked to the cobalamin in a manner that does not disrupt the transfer process. It is important to note that the interior of the vacuole has a proteolytic environment. Therefore, it is necessary to ensure that the biological substance to be given is not vulnerable to the effects of cathepsins. Additionally, it is important to mention that once the vitamin enters the bloodstream, it remains attached to TCII. Therefore, it may be necessary to take

measures to separate the biological component from the cobalamin before the TCII is absorbed by its intended cell.

The Russell-Jones group conducted significant research on utilizing Vitamin B12 transport for delivering biologics. They successfully proved the uptake of several compounds such as GCRF, EPO, and LHRH antagonists. However, it was evident that the system's capabilities were restricted due to the limited density of the cubilin receptor in the ileum. This density only allowed for the absorption of approximately 2 micrograms of Vitamin B12 each day. This is comparable to a maximum of 100 micrograms of peptide or protein, depending on its molecular weight. In order to address this issue, researchers examined the conjugation of Vitamin B12 to microparticles that encapsulate the protein of interest. This approach significantly increased the ratio of protein to ligand, while simultaneously providing protection against protease degradation in the intestinal lumen. Success was attained by utilizing insulin enclosed within dextran nanoparticles measuring 150-300 nm. In streptozotocin-treated rats, a minimum of 5 ug of insulin was absorbed from the gastrointestinal tract, resulting in a 70% decrease in plasma glucose levels. This outcome serves as evidence that the insulin was in a biologically active state. Although it shows promise as a delivery method, it is uncertain whether a cost-effective way to administer enough insulin can be achieved. While the overall bioavailability seems to be around 30%, there may be difficulties in manufacturing, especially in managing and understanding the chemical processes involved. This technique could be applied to peptides that are more potent than insulin, requiring fewer quantities for absorption, and where daily fluctuations in the quantity of Vitamin B12 receptors are not a concern. To obtain a comprehensive overview of the transportation of both small and large compounds using Vitamin B12, refer to the study conducted by Clardy et al.

Biotin

Another gastrointestinal receptor that has been identified as a potential pathway for delivering biologics is the receptor for biotin. Biotin, similar to Vitamin B12, is a necessary component for various biochemical activities in the body. However, mammals cannot produce biotin on their own, therefore they must obtain it from their diet or rely on commensal bacteria in the large intestine to produce it. Regardless of the situation, the receptor responsible is the sodium-dependent multivitamin transporter (SMVT), which is located in the apical membranes of enterocytes, as well as hepatocytes and other cell types. Geho et al. have

developed an insulin delivery system that utilizes biotin as a targeting agent. This system effectively transports insulin through the intestinal cell wall and specifically to the liver cells. The fundamental function of insulin in this context is to regulate glucose levels. The composition is a liposome-like particle, however it remains uncertain whether the insulin is enclosed within the phospholipid envelope or attached/cross-linked to its outside. Significant efficacy was observed in both animals and humans, indicating an uptake rate of 50% or higher. However, accurately determining the level of bioavailability is challenging due to the presence of chromium ions and biotin in the oral formulations used, in addition to insulin. Both chromium ions and biotin are known to enhance the effectiveness of insulin in regulating glucose.

The specific process by which the insulin/biotin combination is taken up is challenging to comprehend. Unlike Vitamin B12, the conjugation of agents to biotin through its free carboxyl group actually hinders the binding and internalization of biotin by enterocytes. The uptake mechanism likely involves a generic process of vacuolation due to the crosslinking of the SMVT on the membrane. This is followed by exocytosis when the vacuole is transported across the enterocyte. The mechanism by which the insulin-coated particle engages with receptors on the hepatocytes' surface remains unknown.

A more significant issue is that biotin not only targets hepatocytes, but also has a tendency to bind to tumors, especially to nascent tumor cells, due to the up-regulation of the biotin receptor in these cells. The potential promotion of cancer is a risk associated with targeting insulin, a well-established growth factor. This could explain why the promising results were not further pursued. To mitigate this potential issue, it would be necessary to develop a method that facilitates the swift separation of the carrier molecule from biotin in the bloodstream. However, it is possible that the current approach may have usefulness in delivering other substances orally, specifically cancer treatments targeted at the liver. Furthermore, it is important to mention that the SMVT receptor, apart from biotin, can also function as a carrier for other lipidic substances including pantothenic acid and lipoic acid. Consequently, it is plausible to consider these molecules as potential targeted ligands for traversing the intestinal barrier.

Bile Salts

Unlike biotin and Vitamin B12, the transportation of bile salts across enterocytes is a constant and rapid process. An adult typically absorbs an average of 18–20 grams each day. The

absorption primarily takes place in the ileum as part of the enterohepatic recycling process. In this process, bile salts, which have completed their role of dissolving fats and lipids in the diet, are transported across the intestinal wall into the portal system. From there, they quickly enter the liver and are directed to the gall bladder for subsequent release into the intestine. This aids in the next cycle of the digestion process.

The Apical Sodium-dependent Bile acid Transporter (ASBT) is the receptor located on the upper surface of enterocytes, responsible for binding bile acids. On the other hand, the secretion of bile salts occurs at the lower surface of enterocytes through the action of OST. ASBT exhibits a wide range of selectivity towards commonly found bile salts. It seems that tiny medication molecules can be attached to either the 3-OH position or the carboxyl group at C-24 without compromising their ability to bind or be taken up. This also applies to peptides, as long as they are extremely short and lipidic. Typically, bigger peptides that have a greater affinity for the receptor are not internalized, despite their ability to bind to it. It is possible to hypothesize that the absorption of bile salt occurs through a mechanism called flip-flop, where it moves across the membrane, rather than through vacuolation like Vitamin B12. This process is hindered by the steric hindrance caused by conjugation with big molecules. Morrison et al. demonstrated successful absorption of a long peptide by attaching gastrin-34 to cholic acid at the C24 position using an amide linkage. They also observed the peptide's biological activity in rats in vivo. The peptide dosage was significantly elevated, although it remains uncertain if the percentage of uptake was adequate to provide a commercially feasible product.

One further concern that must be resolved is the quick separation of the bile salt from the peptide. This is necessary because ASBT is also present on hepatocytes, which could cause the peptide to be redirected to the gall bladder if the two substances are not separated.

Transferrin

Transferrin is a high molecular weight glycoprotein (with a molecular weight of 79.5 kD) that is taken up by several types of cells by receptor-mediated endocytosis. This mechanism helps in the absorption of iron into tissues, where it is utilized for intra-cellular metabolic reactions. Transferrin receptors, including TfR1 and TfR2, serve as two distinct types of receptors for transferrin. TfR1 has high affinity, while TfR2 has low affinity. Researchers have utilized transferrin fusion proteins to specifically target these receptors, aiming to facilitate the delivery of therapeutic biologicals into cells or across cell membranes. The receptors are

excessively expressed in specific types of tumor cells, and the receptor's capacity to facilitate the transportation of transferrin-antibody fusion proteins across the blood-brain barrier has been documented.

There is a disagreement among researchers over the existence of transferrin receptors in the intestine. Some writers propose that these receptors are exclusively located on the basolateral surface of enterocytes, rather than the apical surface. In the case of inflammatory bowel disease (IBD), the receptor may undergo up-regulation or relocation. If transferrin does really have a function in the intestinal tissue, it appears that, unlike in other areas of the body, its activity is not related to the absorption of iron. Instead, it seems to assist in the regulation of immunological tolerance in the intestines.

Transferrin, originally designed for a specific purpose in the intestine, has been examined as a potential vehicle for delivering therapeutic biological substances. This has been done by creating fusion proteins with insulin, pro-insulin, or human growth hormone (GH), all of which have been tested on rats. In the subsequent investigation, the growth hormone (GH) maintained its functionality in the fusion protein as long as it was connected to transferrin across a lengthy helical spacer consisting of 50 amino acids. Following oral treatment, hypophysectomised rats exhibited a slight increase in body weight, indicating that around 2% of the protein was absorbed into the bloodstream. The scientists hypothesized that the growth hormone was being degraded by intestinal proteases, specifically trypsin and chymotrypsin. They suggested that the presence of protease inhibitors could increase the levels of delivery of the growth hormone.

Cholix Cholix is an exotoxin produced by Vibrio cholera that specifically attaches to the lectin mannose-binding protein 1 (LMAN-1) found on the outer layer of enterocytes. Applied Molecular Transport in the United States is actively promoting the use of Cholix to facilitate the absorption of siRNA and proteins. Translocation of fusion proteins containing a shortened, harmless segment of Cholix that maintains its ability to bind to ligands has been demonstrated to occur from the top to the bottom surface of cells via vesicles that contain Rab7+ and Rab11+. The transportation of hGH has been proven through histologic localization and the discovery of an increase in IGF-1 levels in hypophysectomized rats. However, there is currently little information available regarding the efficiency of uptake.

Immunoglobulin Fc

The body contains many Fc receptors that primarily aid immune cells like B cells and dendritic cells in presenting antigens by attaching immunoglobulin molecules to their surface. The receptors are classified as members of the Ig superfamily and have a molecular weight ranging from 50 to 80 kD. In humans, the receptor for IgG is encoded by genes situated on chromosome 1. Another receptor for Fc exists, which mostly aids in the transportation of IgG between polarized cells, such as those found in the kidney, placenta, and intestines. The Fc receptor in question is distinct from other receptors, as it belongs to the MHC family. It has a molecular weight of 41 kD and is found on chromosome 19 in humans. The bacterium was initially obtained from the intestines of newborn rats, where it serves the purpose of transporting maternal IgG antibodies from the intestinal wall into the circulation. This is a crucial step in providing immunity to infants through the consumption of breast milk. The receptor was designated as the neonatal receptor (FcRn), despite its widespread presence in adult individuals.

The FcRn is located in the apical membrane of enterocytes, where it is associated with beta-2 microglobulin. Two FcRn molecules bind to the Fc part of IgG, causing it to be taken up into endocytic vesicles. These vesicles then carry the IgG to the basolateral surface. Under certain circumstances, IgG can move bidirectionally, resulting in a recycling mechanism where antigens in the gut lumen are transported to the lamina propria. This transfer aids in the development of a systemic immune response. The expression of the receptor on intestinal cells can be influenced by agents such as TNF alpha or gamma interferon, resulting in either an increase or decrease in its activity. However, the receptor is consistently present in significant amounts. In normal individuals, it is possible for milligram quantities of IgG to be transferred from the lumen within a day.

Low et al. demonstrated the utilization of this receptor for transporting biologics by creating fusion proteins of the Fc segment with the alpha and beta chains of FSH. The absorption of biologically active protein into the bloodstream was evidenced by the observed rise in the weight of the ovaries/testes in rats, as well as the levels of inhibin in primates. The study did not provide information on the relative bioavailability. However, it did highlight a significant increase in the half-life of the FSH fusion protein compared to FSH alone. In rats, the half-life of the fusion protein was 69 hours, whereas for FSH alone it was 11.4 hours. In primates, the half-life of the fusion protein was over 200 hours, whereas FSH alone had a half-life of

approximately 24 hours. The presence of FcRn in the kidney serves to inhibit the quick excretion of IgG into the urine, so maintaining its circulation within the bloodstream. This action is also seen in other proteins that include the Fc fragment. It provides an additional advantage of administering a biologic orally by utilizing FcRn as a transporter across the intestinal epithelium.

It is important to note that FcRn possesses a specific location for interacting with albumin, enabling it to transport albumin fusion proteins in a similar manner as it does with Fc. These proteins would also gain advantages from the absorptive function of FcRn in the kidney, as it contributes to the extended lifespan of albumin in the bloodstream. Nevertheless, this technique has a drawback in that it results in an enlarged size of the biologic, a payload to carrier ratio of 1:1, and potential interference with the biologic's activity due to the direct fusion of the carrier (Fc or albumin). To address these limitations, researchers have explored the integration of biologics into nanoparticles.

Two investigations have shown that biologics can be effectively delivered by using Fc-coated PLGA nanoparticles as encapsulation agents. Pridgen et al. examined the impact of insulin, whereas Shi and colleagues investigated the influence of exenatide in nanoparticles that closely resembled those used by Pridgen. Both groups observed decreases in blood glucose levels, suggesting that the proteins were fully absorbed, and the extent of the response was in line with an absorption rate of approximately 10%.

Accurate comparisons were challenging due to the significant differences in the pharmacodynamics and pharmacokinetics of ingested particles and injected free protein in both cases. Shi's imaging data indicated that the presence of Fc coating on the particles resulted in a longer retention time in the intestine, ranging from approximately 6 to 12 hours, compared to 4 to 6 hours without the coating. The exact mechanism by which the particles were retained in the intestine is uncertain, but it is possible that they were either attached to the outer surface of the intestinal cells, held within the enterocytes, or trapped in the intestinal lymphatics. It is likely that a combination of these factors contributed to the observed retention. The small size of the particles (100 nm) renders it improbable for them to swiftly go into the portal vein. In contrast, the findings from Pridgen shown that the particles released 50% of their insulin within a time frame of less than two hours. Additionally, the particles exhibited a maximum decrease in glucose levels starting at 4 hours for exenatide and 7-10 hours for insulin, compared to only 1 hour for either peptide when given intravenously.

This strategy appears to be a viable delivery mechanism for biological substances in general. However, it may not be the preferred route for delivering insulin, as it is crucial to prevent excessive amounts of insulin in the bloodstream and instead directly introduce it into the liver through the portal vein.

NON-RECEPTOR-SPECIFIC CHEMICAL METHODS OF ENTRY[22,86]

Numerous oral delivery systems have been developed that do not rely on specific interactions with membrane transport mechanisms. Instead, these systems affect the environment or cells (typically enterocytes) as a whole, causing significant changes that enable the passage of biologics through the intestinal barrier. Due to the ease of processing these compounds using conventional pharmaceutical methods, several of them have advanced to the final stages of clinical studies.

Muco-Adhesion

An approach that has been used is to utilize materials that do not directly interact with the cells of the intestine, but instead interact with the layer of mucus that covers the surface. The idea behind this approach is that by increasing the amount of time the drug stays in the intestine, especially near the gut wall, it allows more time for the drug to be released and diffuse through the mucus layer. This ultimately increases the concentration of the therapeutic agent that is available to cross the cellular barrier.

Several diverse agents have been identified as potential muco-adhesins, which aligns with the complex characteristics of mucin. These characteristics include regions with high concentrations of negative charge, sugar residues, and hydrophobic regions. Shaikh et al. offer a comprehensive overview of the fundamental principles that govern muco-adhesive interactions. Chitosan, a cationic amino-saccharide polymer, is frequently employed as an adhesin. It has the ability to bind to surfaces that carry a negative charge. Additionally, chitosan can be prepared as carriers in the form of microparticles. However, it is important to exercise caution with this method because chitosan is recognized as an effective immune adjuvant. While this is not a problem when using small-molecule medications, it becomes an undesired characteristic when trying to deliver biologics. Many polysaccharides obtained from food have the property of being able to stick to mucus. The tomato lectin, which was initially suggested as a substance that can stick to the membranes of intestinal cells, also has the potential to attach to mucin.

The success of a calcium phosphate particle produced by Biolaxy is attributed to its muco-adhesive qualities. The administration of insulin, enclosed within the particles, resulted in a decrease in glucose levels in patients with type II diabetes, indicating a biopotency ranging from 1% to 5%.

Zhou et al. have recently devised a method to create nanoparticles using cysteine-derivatised alginate. The unbound sulfhydryl groups increase the ability to stick to mucin and subsequently aid in the opening of tight junctions through their effects on F-actin and ZO-1 protein. The particles were employed to encapsulate insulin and glucose oxidase (GO), with the aim of achieving glucose-responsive release of insulin from the polymer by creating a low-oxygen environment through the action of GO in combination with 2-nitro-imidazole. Although a decrease in glucose levels was observed in diabetic rats following the oral administration of particles, it is important to note that a high dose of insulin (75 iu/kg) was used. Furthermore, it remains uncertain if the release of insulin in the body was responsive to changes in glucose levels.

A key contradiction surrounding the muco-adhesive method for delivery of biologics is that muco-adhesins immobilise the vehicle on the upper surface of the mucin layer, keeping it away from the cell surface, rather than improving contact with the enterocytes. Under typical conditions, the unaided diffusion of big molecules across the mucus layer is highly restricted. Furthermore, the mucus layer consistently sheds mucin, along with the carrier, and is replenished by newly generated mucin from goblet cells. As a result, the planned retention at the surface of the intestinal wall may not be as long-lasting. To harness the beneficial muco-adhesive qualities of compounds like the ones mentioned above, it is necessary to include them as supplementary components in formulations that utilize other processes to improve uptake. Illustrations of this phenomenon can be observed in the subsequent section.

Paracellular Transport

Paracellular transport involves the loosening of tight connections between enterocytes, enabling medicines to be transported through water channels that connect the lumenal and serosal compartments. Although certain agents, such as C perfringens toxin, have been mentioned earlier for their ability to open tight junctions by binding to claudin-9, there are numerous other agents that have been extensively studied and act in a less specific manner. Surfactants, for instance, can interact with phospholipid membranes, leading to increased

permeability. This interaction may potentially affect calcium levels in the cytoskeleton, thereby weakening the interaction between tight junction proteins.

Oramed has completed several clinical trials using a formulation consisting of fish oils that contain highly unsaturated fatty acids with fluidizing properties. They claim that this formulation can effectively open tight junctions. The study demonstrated reductions in initial blood glucose levels in individuals with type 1 diabetes who were administered 8 mg of insulin three times daily. Ongoing research is being conducted to advance this formulation for commercialization in patients with type 2 diabetes.

The abundance of highly unsaturated fatty acids may lead to stability concerns due to the potential for oxidation effects. Enclosing hydrophilic proteins within a hydrophobic oil phase is a difficult task, and the method used may resemble the one proposed by New et al. or Wang et al. If insulin remains bound to lipids during its journey to the bloodstream, there is a possibility that it will be retained in the lymphatic system and reach the peripheral circulation through the lumbar duct, instead of directly interacting with the liver. Chiasma has taken a similar strategy by incorporating the short peptide octreotide into an oily surfactant composition. Humans have exhibited biological activity, specifically a decrease in IGF-1 levels, when given a high dosage of at least 40 mg per day.

Several alternative compositions using surfactants as primary constituents have been evaluation in clinical trials. Sodium caprate has long been recognized as a substance that improves permeability. It was included in the initial oral insulin formulation created by Merrion and showed significant results in trials involving type 2 diabetes individuals conducted by Novo Nordisk. Despite the trial yielding favorable results, Novo's oral insulin program was ultimately terminated, reportedly due to economic reasons.

Geranic acid, a type of short-chain fatty acid, has been utilized as a permeation enhancer in transdermal and oral delivery. It is combined with choline as a counter ion, forming a "ionic liquid" known as 'CAGE'. Insulin has demonstrated favorable stability at room temperature when in a dry solid state. However, it should be noted that animal trials utilized capsules containing an aqueous solution, which is not a suitable long-term formulation method. The authors proposed that rats might reach a bioavailability of 50% or higher compared to subcutaneous injection. Additionally, they presented evidence of paracellular transport via Caco-2 cells. The precise contribution of the geranyl content of the formulation to the

observed absorption is uncertain, as is the significance of its presentation as an ionic solution referred to as a 'deep eutectic solvent'. To access a recent analysis on ionic liquids and their impact on live cells, refer to the study conducted by Kumari et al.. It has yet to be determined if the positive outcomes observed in research conducted on small animals can be replicated in humans.

Unigene (now Enteris) was the first to develop a formulation that included acyl carnitines and citric acid. The purpose of citric acid was to maintain the pH of the intestines at 3, which in turn reduced protease activity. The PeptelligenceTM technology shown notable absorption of calcitonin in phase 2 trials, utilizing a daily dosage of 1 mg. Nevertheless, the supplied capsule is of considerable size (size 0) and contains around 1 gram of formulation excipients. Notably, both the active and placebo capsules had significant gastrointestinal effects, most likely attributed to the presence of citric acid, which is known to produce such effects.

Transcellular

Lipidic Pathways

The behavior of amphiphiles in the intestine is a complex and uncertain topic, as their methods of action often extend beyond simply altering membrane fluidity. At lower concentrations, sodium caprate can cause the opening of tight junctions. However, at greater concentrations, it can also facilitate the transport of biologics through the enterocyte plasma membrane. The mechanism behind this phenomenon remains rather ambiguous. One potential explanation is that the amphiphile forms a non-covalent bond with the peptide, which enhances the peptide's hydrophobic properties. This allows the peptide to integrate itself into the lipid core of the cell membrane and subsequently enter the cell's interior through a flip-flop mechanism. Indeed, Emisphere has put forth a technique utilizing its 'Eligen' technology to promote a certain process in a range of compounds. This involves the use of molecules with acronyms like SNAC, CNAC, and CNAB. These molecules are amphiphiles composed of a substituted aromatic core connected through a peptide bond to the omega-end of a short-chain fatty acid, in the form of its sodium salt. Various variations are utilized, each having a distinct peptide. Regarding semaglutide, which was investigated by Novo Nordisk and includes SNAC as an absorption-enhancing agent, a supplementary mechanism for uptake has been suggested. This mechanism involves transcellular uptake in the stomach, which is facilitated by altering the pH or the local microenvironment. The comparison of biological effectiveness with a subcutaneous control indicates that the level of

absorption ranges from 1% to 2.5%. The FDA has previously granted approval to this formulation.

Arisgen, a different company, has developed amphiphiles in the shape of crown ethers that attach to the polar surfaces of proteins, enhancing their hydrophobic properties. Projects using the oral/buccal administration of leuprolide and exenatide are currently being pursued. Biocon likely achieves a comparable outcome by utilizing a technique initially created by Nobex, which has been recently utilized for administering insulin. In this case, the amphiphilic molecules are linked to the protein through direct chemical conjugation. The initial patents utilized short-chain fatty acids, which were connected to lysine side-chains and featured a PEG chain at the omega terminus. In subsequent patents, the arrangement of the lipidic and polar components is reversed, resulting in the protein being connected to a lengthy hydrocarbon chain through a PEG spacer. Furthermore, the lipid chains not only provide protection for the protein against protease assault, but also promote contact with the lipid component of the cell membrane. The covalently-attached hydrocarbon chains have the potential to attract the protein through the lipid-processing pathway by interacting with fatty acid receptors. This can result in vesicular transport across the cell and subsequent secretion with chylomicrons.

The uptake of insulin is highly efficient in both preclinical and human trials. An elevated peak is observed in the serum, prompting speculation about potential reduction in binding to insulin receptors due to chemical changes. The medicine is being marketed as a prandial insulin, specifically designed to mitigate spikes in glucose levels during meal times, as opposed to exerting a prolonged effect on basal levels. The active ingredient, being a modified form of insulin, is considered a novel chemical compound and is therefore subject to strict regulatory standards. However, the clinical trials conducted thus far have not revealed any safety concerns.

The lipid-processing route can be targeted by different vehicles, such as the cholestosome, which aims to integrate medicines and proteins into chylomicrons using a liposome-like vesicle made of cholesterol esters.

Endocytotic Pathway

Diabetology Ltd. has created a formulation that combines a natural bile salt with other excipients that are considered safe for consumption. This formulation has three different

effects that help biologics pass through the intestinal wall. Firstly, it temporarily inhibits proteases to prevent the breakdown of the formulated biologics in the gut. Secondly, it has a mucolytic action that allows better access to cells by breaking down the mucin layer. Lastly, it stimulates cells, causing them to take up proteins through a process called fluid-phase vacuolation. This uptake mechanism is a natural process that allows the absorption of digested nutrients. Normally, it is inactive when a person is fasting, but it can be enhanced by the formulation excipients to enable the intake of intact proteins that have not been broken down by proteases.

The formulation is a desiccated powder, provided in an enteric-coated capsule, which disintegrates in the duodenum to release its contents that quickly dissolve in the watery lumenal fluid. Preclinical investigations have demonstrated that protein levels in peripheral blood exhibit a bioavailability of approximately 10%, but concentrations in the portal vein are considerably greater, thereby confirming it as the primary point of entrance into the body. An investigation using clamps to evaluate the effects of oral insulin in individuals with type 2 diabetes has revealed a prolonged duration of 9-14 hours during which glucose excretion is influenced. These trials showed that the levels of insulin in the peripheral region did not increase beyond the initial level. This suggests that the liver absorbed all of the insulin before it could reach the outer circulation. The formulation exhibits long-term stability at ambient temperature, and no instances of hypoglycemia have been reported in treated individuals. The product is presently undergoing phase 2b clinical studies.

CONCLUSION[1,22]

Despite tremendous advancements, research on the oral administration of biologics has not yet had a substantial influence in clinical settings. The limited success in translating therapeutic applications in this field, which is partly due to the formidable physiological barriers in the gastrointestinal tract (GIT), is sometimes attributed to concerns about the safety of drug delivery methods. Nevertheless, the growing understanding of physiological obstacles, together with remarkable recent advancements in materials, are driving progress in this field and are expected to enable the practical use of oral administration for biologics.[1]

The oral administration of large peptides and proteins has reached a mature stage. Several clinical trials have demonstrated efficacy, indicating that items will likely be available in the market over the next few years. The main obstacles to their availability will be economic and logistical, rather than technical. The expenses associated with the mass production of

biologics have significantly decreased in recent years. The issue of only a fraction of the payload being delivered through the gut is no longer a concern. Biopotency levels as low as 10% are now adequate to produce economically viable products. Although it may be challenging for delivery purposes, the significant proteolytic activity in the gastrointestinal tract ensures that any substance that is not absorbed is quickly degraded into harmless constituents, hence eliminating any safety concerns. The focus now shifts to the characteristics of the vehicle, which can frequently have a far greater significance compared to the API, ranging from 10 to one thousand times. Clearly, excipients that are inexpensive, designated as Generally Recognized as Safe (GRAS) or included in pharmacopoeias, stable, and have a proven track record of safety are highly beneficial. Biologics currently have a significant impact on disease treatment, particularly in the fields of diabetes (insulin, GLP-1), osteoporosis (sCT and PTH), and rheumatoid arthritis (TNF blockade). The introduction of new techniques for administering these medications orally will soon revolutionize the treatment of these chronic conditions, as well as others.[22]

REFERENCES

1. Julia Mantaj, Driton Vllasaliu. Recent advances in the oral delivery of biologics. The pharmaceutical journal. Doi: 10.1211/PJ.2020.20207374.
2. Urquhart L. Top drugs and companies by sales in 2018. Nat Rev Drug Discov., 2019; 18(245). doi: 10.1038/d41573-019-00049-0.
3. 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.
4. 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.
5. 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.
6. GarcÃa-PÃ©rez 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.
7. Gedawy A, Martinez J, Al-Salami H & Dass CR. Oral insulin delivery: existing barriers and current counter-strategies. J Pharm Pharmacol, 2018; 70(2): 197–213. doi: 10.1111/jphp.12852.

8. Harrison GA. Insulin in alcoholic solution by the mouth. BMJ, 1923; 2(3286): 1204–1205. doi: 10.1136/bmj.2.3286.1204.
9. Murlin JR, Sutter CC, Allen RS & Piper HA. Some favorable effects from the alimentary administration of insulin. Endocrinology, 1924; 8(3): 331–339. doi: 10.1210/endo-8-3-331.
10. Salen E. Einige Versuche mit peroraler Darreichung von Insulin [Attempts with oral insulin administration]. Acta Medica Scandinavica, 1924; 60(1): 74–87. doi: 10.1111/j.0954-6820.1924.tb15268.x.
11. 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.
12. Mantaj J, Abu-Shams T, Enlo-Scott Z et al. Role of the basement membrane as an intestinal barrier to absorption of macromolecules and nanoparticles. Mol Pharm, 2018; 15(12): 5802–5808. doi: 10.1021/acs.molpharmaceut.8b01053.
13. Vllasaliu D, Falcone FH, Stolnik S & Garnett M. Basement membrane influences intestinal epithelial cell growth and presents a barrier to the movement of macromolecules. Exp Cell Res., 2014; 323(1): 218–231. doi: 10.1016/j.yexcr.2014.02.022.
14. Mahato RI, Narang AS, Thoma L & Miller DD. Emerging trends in oral delivery of peptide and protein drugs. Crit Rev Ther Drug Carrier Syst., 2003; 20(2–3): 153–214. doi: 10.1615/critrevtherdrugcarriersyst.v20.i23.30.
15. Maher S, Ryan B, Duffy A & Brayden DJ. Formulation strategies to improve oral peptide delivery. Pharm Pat Anal, 2014; 3(3): 313–336. doi: 10.4155/ppa.14.15.
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. Vllasaliu D, Thanou M, Stolnik S & Fowler R. Recent advances in oral delivery of biologics: nanomedicine and physical modes of delivery. Expert Opin Drug Deliv, 2018; 15(8): 759–770. doi: 10.1080/17425247.2018.1504017.
18. McCartney F, Gleeson JP & Brayden DJ. Safety concerns over the use of intestinal permeation enhancers: a mini-review. Tissue Barriers, 2016; 4(2): e1176822. doi: 10.1080/21688370.2016.1176822.
19. Traverso G, Schoellhammer CM, Schroeder A et al. Microneedles for drug delivery via the gastrointestinal tract. J Pharm Sci., 2015; 104(2): 362–367. doi: 10.1002/jps.24182.

20. Binit Patel, Archita Patel, Dilip Ghava, Rikeeta Padiya, Pravinkumar Darji, 2023. Development and validation of stability indicating rp-hplc method for estimation of cyclandelate in bulk drug and capsule dosage form. Journal of medical pharmaceutical and allied sciences, 2023; 12(6): 6247-6253. Doi: https://doi.org/10.55522/jmpas.V12I6.5943.
21. Pravinkumar Darji, Jayendrakumar Patel, Binit Patel, Shalin Parikh, Praneeth Ivan Joel FNU. Overview on osmotic drug delivery system. International journal of pharmaceutical research and applications, Jan-Feb 2024; 9(1): 86-100. DOI: 10.35629/7781-090186100.
22. Proxima Concepts Ltd., Faculty of science and Technology. Oral delivery of biologics via the intestine. MDPI. Pharmaceutics, 2021; 13(1): 18. https://doi.org/10.3390.
23. Barbosa J.A.C., Al-Kauraishi M.M., Smith A.M., Conway B.R., Merchant H.A. Achieving gastroresistance without coating: Formulation of capsule shells from enteric polymers. Eur. J. Pharm. Biopharm. 2019; 144: 174–179. doi: 10.1016/j.ejpb.2019.09.015. [PubMed] [CrossRef] [Google Scholar]
24. Kararli T.T. Comparison of the gastrointestinal anatomy, physiology, and biochemistry of humans and commonly used laboratory animals. Biopharm. Drug Dispos, 1995; 16: 351–380. doi: 10.1002/bdd.2510160502. [PubMed] [CrossRef] [Google Scholar]
25. Vighi G., Marcucci F., Sensi L., Di Cara G., Frati F. Allergy and the gastrointestinal system. Clin. Exp. Immunol, 2008; 153: 3–6. doi: 10.1111/j.1365-2249.2008.03713.x. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
26. New R. Formulation technologies for oral vaccines. Clin. Exp. Immunol, 2019; 198: 153–169. doi: 10.1111/cei.13352. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
27. Saurer L., Mueller C. T cell-mediated immunoregulation in the gastrointestinal tract. Allergy, 2009; 64: 505–519. doi: 10.1111/j.1398-9995.2009.01965.x. [PubMed] [CrossRef] [Google Scholar]
28. Ruberti M., Fernandes L.G.R., Simioni P.U., Gabriel D.L., Yamada A.T., Tamashiro W.M.C. Phenotypical and functional analysis of intraepithelial lymphocytes from small intestine of mice in oral tolerance. Clin. Dev. Immunol, 2012; 2012: 1–16. doi: 10.1155/2012/208054. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
29. Awaad A., Nakamura M., Ishimura K. Imaging of size-dependent uptake and identification of novel pathways in mouse Peyer's patches using fluorescent organosilica particles. Nanomedicine, 2012; 8: 627–636. doi: 10.1016/j.nano.2011.08.009. [PubMed] [CrossRef] [Google Scholar]

30. Florence A.T., Hillery A.M., Hussain N., Janu P.U. Uptake and translocation of nanoparticles: A real but useful phenomenon? In: Gregoriadis G., McCormack P., Poste G., editors. Targeting of Drugs 4. Volume 273. Springer; Boston, MA, USA, 1994; 173–181. (NATO ASI Series (Series A: Life Sciences)). [Google Scholar]
31. Dressman B.J., Reppas C. In vitro-in vivo correlations for lipophilic, poorly water-soluble drugs. Eur. J. Pharm. Sci., 2000; 11: S73–S80. doi: 10.1016/S0928-0987(00)00181-0. [PubMed] [CrossRef] [Google Scholar]
32. Wang J., Yadav V., Smart A.L., Tajiri S., Basit A.W. Toward Oral Delivery of Biopharmaceuticals: An Assessment of the Gastrointestinal Stability of 17 Peptide Drugs. Mol. Pharm, 2015; 12: 966–973. doi: 10.1021/mp500809f. [PubMed] [CrossRef] [Google Scholar]
33. Bansil R., Turner B.S. Mucin structure, aggregation, physiological functions and biomedical applications. Curr. Opin. Colloid Interface Sci., 2006; 11: 164–170. doi: 10.1016/j.cocis.2005.11.001. [CrossRef] [Google Scholar]
34. Ambort D., Johansson M.E.B., Gustafsson J.K., Ermund A., Hansson G.C. Perspectives on Mucus Properties and Formation—Lessons from the Biochemical World. Cold Spring Harb. Perspect. Med., 2012; 2: a014159. doi: 10.1101/cshperspect.a014159. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
35. Nilsson H.E., Ambort D., Bäckström M., Thomsson E., Koeck P.J.B., Hansson G.C., Hebert H. Intestinal MUC2 mucin supramolecular topology by packing and release resting on D3 domain assembly. J. Mol. Biol., 2014; 426: 2567–2579. doi: 10.1016/j.jmb.2014.04.027. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
36. Javitt G., Khmelnitsky L., Albert L., Bigman L.S., Elad N., Morgenstern D., Ilani T., Levy Y., Diskin R., Fass D. Assembly Mechanism of Mucin and von Willebrand Factor Polymers. Cell, 2020; 183: 717–729. doi: 10.1016/j.cell.2020.09.021. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
37. Madara J.I., Trier J.S. The Functional Morphology of the Mucosa of the Small Intestine. In: Johnson L.R., editor. Physiology of the Gastrointestinal Tract. Raven Press; New York, NY, USA: 1994. [Google Scholar]
38. Thomson A., Cheeseman C., Keelan M., Fedorak R.N., Clandinin M. Crypt Cell Production Rate, Enterocyte Turnover Time and Appearance of Transport along the Jejunal Villus of the Rat. Biochim. Biophys. Acta, 1994; 1191: 197–204. doi: 10.1016/0005-2736(94)90249-6. [PubMed] [CrossRef] [Google Scholar]

39. Munkholm P., Langholz E., Hollander D., Thornberg K., Orholm M., Katz K.D., Binder V. Increased Intestinal Permeability in Patients with Crohn's Disease and Their Healthy Relatives. Ann. Int. Med., 1986; 105: 883–885. [PubMed] [Google Scholar]
40. Ryan C.M., Yarmush M.L., Tomkins R.G. Separation and Quantitation of Polyethylene Glycols 400 and 3350 from Human Urine by High Performance Liquid Chromatography. J. Pharm. Sci., 1992; 81: 350–352. doi: 10.1002/jps.2600810412. [PubMed] [CrossRef] [Google Scholar]
41. Lane M.E., O'Driscoll C.M., Corrigan O.I. The Relationship between Rat Intestinal Permeability and Hydrophilic Probe Size. Pharm. Res., 1996; 13: 1554–1558. doi: 10.1023/A:1016091915733. [PubMed] [CrossRef] [Google Scholar]
42. Ryan A.J., Chang R.T., Gisolfi C.V. Gastro-intestinal Permeability following Aspirin Intake and Prolonged Running. Med. Sci. Sports Exerc., 1996; 28: 698–705. doi: 10.1097/00005768-199606000-00009. [PubMed] [CrossRef] [Google Scholar]
43. Sigthorsson G., Tibble J., Hayllar J., Menzies I., MacPherson A., Moots R., Scott D., Gumpel M.J., Bjarnason I. Intestinal permeability and Inflammation in Patients on NSAIDs. Gut., 1998; 43: 506–511. doi: 10.1136/gut.43.4.506. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
44. Kvietys P.R., Specian R.D., Grisham M.B., Tso P. Jejunal Mucosal Injury and Restitution: Role of Hydrolytic Products of Food Digestion. Am. J. Physiol., 1991; 261: G381–G391. doi: 10.1152/ajpgi.1991.261.3.G384. [PubMed] [CrossRef] [Google Scholar]
45. Matovelo J.A., Landsverk T., Sund R.B. Enzyme Changes in Remodelling Epithelial Cells: A Histochemical Study of the Rat Jejunum in vivo during and Following Exposure to Deoxycholic Acid. APMIS, 1993; 101: 369–377. doi: 10.1111/j.1699-0463.1993.tb00123.x. [PubMed] [CrossRef] [Google Scholar]
46. Breslin N.P., Price L.M., Medding J.B., Sutherland L.R. Intestinal Permeability is Increased in a Proportion of Spouses of Patients with Crohn's Disease. Am. J. Gastroenterol, 2001; 96: 934–938. doi: 10.1111/j.1572-0241.2001.04684.x. [PubMed] [CrossRef] [Google Scholar]
47. Soderholm J., Olaison G., Lindberg E., Hannestad U., Vindels A., Tysk C., Jarnerot G., Sjodahl R. Different Intestinal Permeability Patterns in Relatives and Spouses of Patients with Crohn's Disease: An Inherited Defect in Mucosal Defence? Gut., 1999; 44: 96–1000. doi: 10.1136/gut.44.1.96. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
48. Suenaga K., Yokoyama Y., Nishimori I., Sano S., Morita M., Okazaki K., Onishi S. Serum Antibodies to Mycobacterium paratuberculosis in Patients with Crohn's Disease. Dig.

Dis. Sci., 1999; 44: 1202–1207. doi: 10.1023/A:1026692627460. [PubMed] [CrossRef] [Google Scholar]

49. Russell-Jones G., Westwood S., Habberfield A. Vitamin B12 mediated oral delivery systems for granulocyte-colony stimulating factor and erythropoietin. Bioconjugate Chem., 1995; 6: 459–465. doi: 10.1021/bc00034a016. [PubMed] [CrossRef] [Google Scholar]
50. Russell-Jones G., Westwood S., Farnworth P., Findlay J., Burger H.G. Synthesis of LHRH antagonists suitable for oral administration via the vitamin B12 uptake system. Bioconjugate Chem., 1995; 6: 34–42. doi: 10.1021/bc00031a600. [PubMed] [CrossRef] [Google Scholar]
51. Chalasani K.B., Russell-Jones G.J., Jain A.K., Diwan P.V., Jain S.K. Effective oral delivery of insulin in animal models using vitamin B12-coated dextran nanoparticles. J. Control. Release, 2007; 122: 141–150. doi: 10.1016/j.jconrel.2007.05.019. [PubMed] [CrossRef] [Google Scholar]
52. Clardy S.M., Allis D.G., Fairchild T.J., Doyle R.P. Vitamin B12 in drug delivery: Breaking through the barriers to a B12 bioconjugate pharmaceutical. Expert Opin. Drug Deliv, 2010; 8: 127–140. doi: 10.1517/17425247.2011.539200. [PubMed] [CrossRef] [Google Scholar]
53. Geho W.B., Geho H.C., Lau J.R., Gana T.J. Hepatic-Directed Vesicle Insulin: A Review of Formulation Development and Preclinical Evaluation. J. Diabetes Sci. Technol., 2009; 3: 1451–1459. doi: 10.1177/193229680900300627. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
54. Geho W.B., Rosenberg L.N., Schwartz S.L., Lau J.R., Gana T.J. A Single-blind, Placebo-controlled, Dose-ranging Trial of Oral Hepatic-directed Vesicle Insulin Add-on to Oral Antidiabetic Treatment in Patients with Type 2 Diabetes Mellitus. J. Diabetes Sci. Technol., 2014; 8: 551–559. doi: 10.1177/1932296814524871. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
55. Hofmann A.F. The continuing importance of bile acids in liver and intestinal disease. Arch. Intern. Med., 1999; 159: 2647–2658. doi: 10.1001/archinte.159.22.2647. [PubMed] [CrossRef] [Google Scholar]
56. Balakrishnan A., Polli J.E. Apical Sodium Dependent Bile Acid Transporter (ASBT, SLC10A2): A Potential Prodrug Target. Mol. Pharm., 2006; 3: 223–230. doi: 10.1021/mp060022d. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

57. Dawson P.A., Karpen S.J. Intestinal Transport and Metabolism of Bile Acids. J. Lipid Res., 2015; 56: 1085–1099. doi: 10.1194/jlr.R054114. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
58. Kramer W., Wess G., Neckermann G., Schubert G., Fink J., Girbig F., Gutjahr U., Kowalewski S., Baringhaus K.H., Böger G. Intestinal Absorption of Peptides by Coupling to Bile Acids. J. Biol. Chem., 1994; 269: 10621–10627. doi: 10.1016/0270-9139(93)92720-K. [PubMed] [CrossRef] [Google Scholar]
59. Swaan P.W., Hillgren K.M., Szoka F.C., Oie S. Enhanced transepithelial transport of peptides by conjugation to cholic acid. Bioconjug Chem., 1997; 8: 520–525. doi: 10.1021/bc970076t. [PubMed] [CrossRef] [Google Scholar]
60. Shin S.U., Friden P., Moran M., Olson T., Kang Y.S., Pardridge W.M., Morrison S.L. Transferrin-antibody fusion proteins are effective in brain targeting. Proc. Natl. Acad. Sci. USA, 1995; 92: 2820–2824. doi: 10.1073/pnas.92.7.2820. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
61. Tang X., Fang M., Xu K., Cheng R., Wang G., Liao Z., Zhang Z., Mwangi J., Lu Q., Lai R. Transferrin-dependent crosstalk between the intestinal tract and commensal microbes contributes for immune tolerance. Bio Rxiv., 2020 doi: 10.1101/2020.03.02.972281. [CrossRef] [Google Scholar]
62. Xia C.L., Wang J., Shen W.C. Hypoglycemic Effect of Insulin-Transferrin Conjugate in Streptozotocin-Induced Diabetic Rats. J. Pharm. Exp., 2000; 295: 594–600. [PubMed] [Google Scholar]
63. Chen Y.S., Zaro J.L., Zhang D.S., Huang N., Simon A., Shen W.C. Characterization and Oral Delivery of Proinsulin-Transferrin Fusion Protein Expressed Using ExpressTec. Int. J. Mol. Sci., 2018; 19: 378. doi: 10.3390/ijms19020378. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
64. Amet N., Wang W., Shen W.C. Human Growth Hormone–Transferrin Fusion Protein for Oral Delivery in Hypophysectomized Rats. J. Control. Release, 2010; 141: 177. doi: 10.1016/j.jconrel.2009.09.007. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
65. Taverner A., Mackay J., Laurent F., Hunter T., Liu K., Mangat K., Song L., Seto E., Postlethwaite S., Alam A., et al. Cholix protein domain I functions as a carrier element for efficient apical to basal epithelial transcytosis. Tissue Barriers, 2020; 8: e1710429. doi: 10.1080/21688370.2019.1710429. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

66. Pyzik M., Sand K.M.K., Hubbard J.J., Andersen J.T., Sandlie I., Blumberg R.S. The Neonatal Fc Receptor (FcRn): A Misnomer? Front. Immunol, 2019; 10: 1540. doi: 10.3389/fimmu.2019.01540. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
67. Kuo T.T., Baker K., Yoshida M., Qiao S.-W., Aveson V.G., Lencer W.I., Blumberg R.S. Neonatal Fc Receptor: From Immunity to Therapeutics. J. Clin. Immunol, 2010; 30: 777–789. doi: 10.1007/s10875-010-9468-4. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
68. Low S.C., Nunes S.L., Bitonti A.J., Dumont J.A. Oral and pulmonary delivery of FSH–Fc fusion proteins via neonatal Fc receptor-mediated transcytosis. Hum. Reprod, 2005; 20: 1805–1813. doi: 10.1093/humrep/deh896. [PubMed] [CrossRef] [Google Scholar]
69. Pridgen E.M., Alexis F., Kuo T.T., Levy-Nissenbaum E., Karnik R., Blumberg R.S., Langer R., Farokhzad O.C. Transepithelial Transport of Fc -Targeted Nanoparticles by the Neonatal Fc Receptor for Oral Delivery. Sci. Transl. Med., 2013; 5: 167. doi: 10.1126/scitranslmed.3007049. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
70. Shi Y., Sun X., Zhang L., Sun K., Li K., Li Y., Zhang Q. Fc-modified exenatide-loaded nanoparticles for oral delivery to improve hypoglycemic effects in mice. Sci. Rep., 2018; 8: 726. doi: 10.1038/s41598-018-19170-y. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
71. Shaikh R., Raj Singh T.R., Garland M.J., Woolfson A.D., Donnelly R.F. Mucoadhesive drug delivery systems. J. Pharm. Bioall Sci., 2011; 3: 89–100. doi: 10.4103/0975-7406.76478. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
72. Cook S.L., Bull S.P., Methven L., Parker J.K., Khutoryanskiy V.V. Mucoadhesion: A food perspective. Food Hydrocoll, 2017; 72: 281–296. doi: 10.1016/j.foodhyd.2017.05.043. [CrossRef] [Google Scholar]
73. Lehr C.-M., Bouwstra J.A., Kok W., Noach A.B.J., de Boer A.G., Junginger H.E. Bioadhesion by Means of Specific Binding of Tomato Lectin. Pharm. Res., 1992; 9: 547–553. doi: 10.1023/A:1015804816582. [PubMed] [CrossRef] [Google Scholar]
74. Zhou X., Wu H., Long R., Wang S., Huang H., Xia Y., Wang P., Lei Y., Cai Y., Cai D., et al. Oral delivery of insulin with intelligent glucose-responsive switch for blood glucose regulation. J. Nanobiotechnol, 2020; 18: 96–112. doi: 10.1186/s12951-020-00652-z. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

75. Eldor R., Arbit E., Corcos A., Kidron M. Glucose-Reducing Effect of the ORMD-0801 Oral Insulin Preparation in Patients with Uncontrolled Type 1 Diabetes: A Pilot Study. PLoS ONE, 2013; 8: e59524. doi: 10.1371/journal.pone.0059524. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
76. New R.R.C., Kirby C.J. Solubilisation of hydrophilic drugs in oily formulations. Adv. Drug Deliv. Rev. 1997; 25: 59–69. doi: 10.1016/S0169-409X(96)00491-7. [CrossRef] [Google Scholar]
77. Wang T., Wang N., Hao A.J., He X., Li T.F., Deng Y.J. Lyophilisation of water-in-oil emulsions to prepare phospholipid-based anhydrous reverse micelles for oral peptide delivery. Eur. J. Pharm. Sci., 2010; 39: 373–379. doi: 10.1016/j.ejps.2010.01.006. [PubMed] [CrossRef] [Google Scholar]
78. Melmed S., Popovic V., Bidlingmaier M., Mercado M., Van Der Lely A.J., Biermasz N., Bolanowski M., Coculescu M., Schopohl J., Racz K., et al. Safety and Efficacy of Oral Octreotide in Acromegaly: Results of a Multicenter Phase III Trial. J. Clin. Endocrinol. Metab., 2015; 100: 1699–1708. doi: 10.1210/jc.2014-4113. [PubMed] [CrossRef] [Google Scholar]
79. Twarog C., Fattah S., Heade J., Maher S., Fattal E., Brayden D.J. Intestinal Permeation Enhancers for Oral Delivery of Macromolecules: A Comparison between Salcaprozate Sodium (SNAC) and Sodium Caprate (C10) Pharmaceutics. 2019; 11: 78. doi: 10.3390/pharmaceutics11020078. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
80. Banerjee A., Ibsen K., Brown T., Chen R.W., Agatemor C., Mitragotri S. Ionic liquids for oral insulin delivery. PNAS, 2018; 115: 7296–7301. doi: 10.1073/pnas.1722338115. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
81. Kumari P., Pillai V.V.S., Benedetto A. Mechanisms of action of ionic liquids on living cells: The state of the art. Biophys. Rev., 2020; 12: 1187–1215. doi: 10.1007/s12551-020-00754-w. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
82. Malkov D., Angelo R., Wang H.Z., Flanders E., Tang H., Gomez-Orellana I. Oral Delivery of Insulin with the eligen® Technology: Mechanistic Studies. Curr. Drug Deliv. 2005; 2: 191–197. doi: 10.2174/1567201053586001. [PubMed] [CrossRef] [Google Scholar]
83. Zinman B., Aroda V.R., Buse J.B., Cariou B., Harris S.B., Hoff S.T., Pedersen K.B., Tarp-Johansen M.J., Araki E. Efficacy, Safety, and Tolerability of Oral Semaglutide Versus

Placebo Added to Insulin With or Without Metformin in Patients With Type 2 Diabetes: The PIONEER 8 Trial. Diabetes Care. 2019; 42: 2262–2271. doi: 10.2337/dc19-0898. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

84. Buckley S.T., Bækdal T.A., Vegge A., Maarbjerg S.J., Pyke C., Ahnfelt-Rønne J., Madsen K.G., Schéele S.G., Alanentalo T., Kirk R.K., et al. Transcellular stomach absorption of a derivatized glucagon-like peptide-1 receptor agonist. Sci. Transl. Med., 2018; 10: eaar7047. doi: 10.1126/scitranslmed.aar7047. [PubMed] [CrossRef] [Google Scholar]
85. Davies M.D., Pieber T.R., Hartoft-Nielsen M.-L., Hansen O.K.H., Jabbour S., Rosenstock J. Effect of Oral Semaglutide Compared With Placebo and Subcutaneous Semaglutide on Glycemic Control in Patients with Type 2 Diabetes A Randomized Clinical Trial. JAMA, 2017; 318: 1460–1470. doi: 10.1001/jama.2017.14752. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
86. Khedkar A., Lebovitz H., Fleming A., Cherrington A., Jose V., Athalye S.N., Vishweswaramurthy A. Pharmacokinetics and Pharmacodynamics of Insulin Tregopil in Relation to Premeal Dosing Time, Between Meal Interval, and Meal Composition in Patients with Type 2 Diabetes Mellitus. Clin. Pharmacol. Drug Dev., 2020; 9: 74–86. doi: 10.1002/cpdd.730. [PMC free article] [PubMed] [CrossRef] [Google Scholar]