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Review

Formulating the Un-drawable: Pharmaceutical Strategies for the Oral Delivery of Biologics (Peptides, Proteins, and Antibodies) and Their Pharmacological Challenges

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Abstract

The use of biologic therapeutics such as peptides, proteins, and monoclonal antibodies is a paradigm shift in the context of modern medicine, and is almost limited to the parenteral route of administration. The gastrointestinal (GI) tract is a potent array of successive biochemical, physical, and cellular obstacles, which implies that less than 1% of the oral bioavailability is attained. This review analytically breaks down these barriers and gives a detailed account of the pharmaceutical strategies, i.e. chemical, nanocarrier, and mechanical that have been engineered to surmount these barriers. We compare the divergent action of clinically approved permeation enhancers (PEs) where gastric absorption, SNAC (salcaprozate sodium) and intestinal, paracellular absorption, MCFAs are contrasted. We examine these highly sophisticated nanocarrier vehicles, describing some of their designs as, for example, the use of a 'Zwitterionic' particle, which solves the 'stick versus slip' paradox with successive penetration into the mucus and interaction with epithelial transporters. We also look at the new technology of ingestible mechanical nanoparticle delivery systems, and microneedle capsules (LUMI) and self-orienting auto-injectors (L-SOMA) that can realize got of injection-like bioavailability (up to 80%) by circumventing the GI barriers physically. Last but not least, the key pharmacological issues that are critically assessed in this review are bioavailability, variability, immunogenicity, and long-term toxicology safety of deliberately and temporarily interfering with the intestinal barrier. The latest clinical advances have shown that oral biologic delivery is now no longer a theoretical possibility, but a clinical fact that places the field at a decisive turning point in terms of therapeutic innovation.

Keywords: Oral Biologic Delivery; Peptide Therapeutics; Protein Formulation; Nanocarriers; Permeation Enhancers; Microneedle Capsule; Salcaprozate Sodium (SNAC); Bioavailability; Tight Junctions; Monoclonal Antibodies.

1. INTRODUCTION:

The Imperative for Oral Biologics

The use of biologic therapeutics such as peptides, proteins, and monoclonal antibodies is a paradigm shift in the context of modern medicine, and is almost limited to the parenteral route of administration. The gastrointestinal (GI) tract is a potent array of successive biochemical, physical, and cellular obstacles, which implies that less than 1% of the oral bioavailability is attained. This review analytically breaks down these barriers and gives a detailed account of the pharmaceutical strategies, i.e. chemical, nanocarrier, and mechanical that have been engineered to surmount these barriers. We compare the divergent action of clinically approved permeation enhancers (PEs) where gastric absorption, SNAC (salcaprozate sodium) and intestinal, paracellular absorption, MCFAs are contrasted. We examine these highly sophisticated nanocarrier vehicles, describing some of their designs as, for example, the use of a 'Zwitterionic' particle, which solves the 'stick versus slip' paradox with successive penetration into the mucus and interaction with epithelial transporters. We also look at the new technology of ingestible mechanical nanoparticle delivery systems, and microneedle capsules (LUMI) and self-orienting auto-injectors (L-SOMA) that can realize got of injection-like bioavailability (up to 80%) by circumventing the GI barriers physically. Last but not least, the key pharmacological issues that are critically assessed in this review are bioavailability, variability, immunogenicity, and long-term toxicology safety of deliberately and temporarily interfering with the intestinal barrier. The latest clinical advances have shown that oral biologic delivery is now no longer a theoretical possibility, but a clinical fact that places the field at a decisive turning point in terms of therapeutic innovation.

2. THE GREAT WALL: A MULTI-LAYERED ANALYSIS OF GI BARRIERS

Oral biologic delivery failure does not occur as a result of a solitary barrier, but rather as a cascade of failure whereby sequential and synergistic barriers act to dispose, block, and repel these molecules. An effective plan should deal with each of them.

2.1 Luminal Gauntlet: Biochemical Barriers.

Prior to the absorption of any biologic, it has to pass the lumen. The initial obstacle is the extreme pH of the stomach which varies between the pH 1.0 and 3.0 when in the fasted state. The extreme acidic conditions result in quick pH-mediated hydrolysis and denaturation of the complex tertiary and quaternary structures required by a protein to be effective as a therapeutic agent.

At the same time, the biologic is exposed to a "gauntlet" of strong potent proteolytic enzymes that are capable of breaking down proteins into their amino acids. It is initiated at the stomach level by the action of pepsin (which is most active at low pH) and then at the small intestine by cascade of pancreatic enzymes, such as trypsin, chymotrypsin, elastase and carboxypeptidase, etc

2.2 Mucus Barrier: A Changeable Physical Obstacle.

The next barrier is the luminal gauntlet which is followed by mucus barrier which is a viscoelastic gel layer that covers the epithelium. It is a not a passive barrier but a biological sieve which is 40-450 um thick in the stomach. It is a net negative glycoprotein (mucins) and thus it entraps and removes cationic molecules via electrostatic interaction, and this is typical of most drug carriers. Moreover, the mucus layer is under constant turnover with the effect of a conveyor belt, which entraps foreign substances such as the nanocarriers and eliminates them before they are permitted to contact the absorptive epithelium.

2.3 The Epithelial Barrier: The First Absorptive Blockade.

The last and the most significant obstacle is the epithelial wall, which is a monolayer of enterocytes that creates the main physical barrier between the gut lumen and the systemic circulation. This is a barrier that offers two main absorption routes that are unfavorable to biologics.

The Transcellular Route: This route is the one that is absorbed into the epithelial cell. This is the main pathway of small, lipophilic molecules that are able to come across the lipid-rich cell membrane. Large (measured in kilodaltons, kDa) and hydrophilic in vivo agents (biologics) are effectively excluded in this pathway.

The Paracelsular Route: It is an absorption between the epithelial cells. This pathway is blocked by intricate protein networks that are known as Tight Junctions (TJs. TJs are size-restrictive gatekeepers of the paracellsular transport, which have effective pore radii of under 1 nm. This practically restricts passive diffusion to molecules smaller than about 700 Da, which forbids peptides, proteins and antibodies.

Should a biologic manage to get across this membrane, it is subject to a last line of defense active efflux transporters. One of the members of the ABC transporter family is p-glycoproteins (P-gp) which is expressed on the apical (luminal) surface of enterocytes and serves as a "bouncer" to actively recapture and pump back xenobiotics into the intestinal lumen of a cell.

It is a series of breakdowns; denaturation by acid, digestion by enzymes, entrapment by mucus, exclusion by TJs, and ejection by efflux pumps that lead to the nearly zero bioavailability of most biologics. The central problem of this cascade is also the development of a series of necessary surface properties, which are antagonistic to the following surface-property necessary to pass the next barrier. An illustration is a nanocarrier, which is inspired to be mucoadhesive (mucoadhesive "stick" in other words) to enhance residence time, but by design it cannot penetrate mucus (mucoadhesive). An anionic mucus layer will first trap a carrier which is cationic to react with the anionic cell membrane. To resolve this dilemma, there is the need to come upwith multi-modal and advanced solutions.

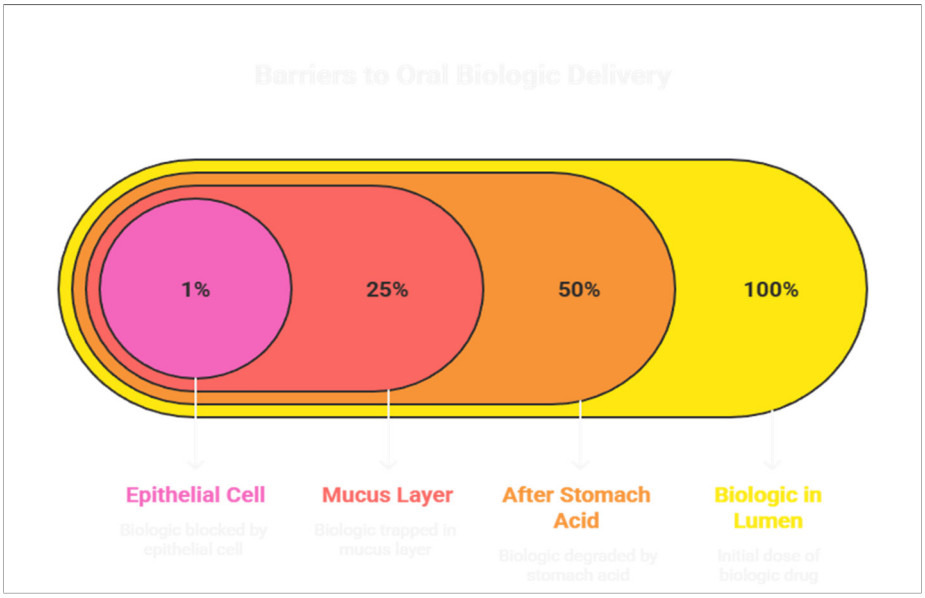

Figure 1. A schematic diagram illustrating the sequential "cascade of failure" for an orally administered biologic. The drug must survive (1) biochemical degradation from acid and enzymes in the lumen, (2) the "biological sieve" of the mucus layer, and (3) the "absorptive blockade" of the epithelial cell layer, which is impenetrable via both transcellular (due to size/hydrophilicity) and paracellular (due to tight junctions) routes.

3. PHARMACEUTICAL STRATEGIES I: EXCIPIENT-BASED AND CHEMICAL FORMULATIONS.

The initial significant paradigm on oral biologic delivery is the co-formulation of the drug with functional excipients. These assistants are meant to chemically and temporarily disable certain GI boundaries.

3.1 Protease Inhibitors (PIs)

An easy solution to reverse the effect of the luminal gauntlet (Section 2.1) is to co-administer protease inhibitors (PIs). Such agents include aprotinin (trypsin inhibitor), leupeptin and soybean trypsin inhibitor, and they are aimed at disarming the scissors, that is, by inhibiting luminal and brush-border proteases.

Although this is an effective strategy in vitro, it has a high pharmacological risk. These non specific inhibitors therefore can affect normal food digestion. Worse still, in the long run, with chronic, continuous PIs usage, there are also serious side effects, like unstable food digestion, which is the most frightening, the second, much more troubling, is that of hypertrophy or hyperplasia of the pancreas. This unacceptable chronic long-term toxicity profile renders PIs an inadvisable mono-modality in the chronic diseases that biologics typically treat.

3.2 Permeation Enhancers (PEs)

The use of permeation enhancers (PEs) would be a better and more successful and clinically validated strategy. PEs are chemical compounds that nonspecifically, and more importantly, temporarily augment intestinal epithelial permeability, permitting the biologic to bypass the barrier through. The FDA approved oral peptides, Rybelsus(r) and Mycapssa(r), two landmark products in the field of decadal research and fully reliant on its proprietary PE technology. Interestingly, the two success stories use vastly different mechanisms, which demonstrates that there are numerous ways to success.

Case Study: The Eligen(r) Technology (SNAC).

Approval of the first oral GLP-1 receptor agonist, Rybelsus(r) (oral semaglutide) was a watershed moment. Its performance is based on the Eligen(r) technology that employs the excipient Salcaprozate Sodium

(SNAC), or sodium 8-[(2-hydroxybenzoyl)amino]octanoate. The SNAC mechanism is multimodal, complicated, and different compared to traditional PEs.

Site of Action: SNAC promotes absorption in the stomach unlike the classic methods of small intestine. This is counter intuitive because stomach surface area is limited and it is not an important site of absorption.

Protection: SNAC is a local buffer. It also counterbalances pH of the micro-environment of the breaking tablet and prevents the hydrolysis of the semaglutide payload in acid and degradation of pepsin.

Permeation: SNAC facilitates absorption (through the cell) rather than paracellular. It is suggested to temporarily permeabilize the gastric cell membrane and serve as a non-covalent carrier.

Localization: The the effect is very short lived and localized. Pre-clinical investigations indicate that drug concentration is 10-fold larger immediately under the tablet, and a model of sedimentation of a tablet was supported, where the absorption was at the point of contact.

The dose schedule of Rybelsus (r) is an obvious manifestation of this vulnerability. The pills should be eaten when the stomach is empty (to enable the formation of a sediment), the amount of water should be not more than 4 ounces (to avoid the dilution of the local concentration-dependent effect), and the patient should wait 30 minutes, without eating or taking other medications. It will give time to the gastric absorption process to take place before food neutralizes the stomach or the gastric emptying pushes the pill to the intestine, where the mechanism is not effective.

Case Study: TPE(r) and GIPET Technology (MCFAs) 3.2.2.

In a sharp contrast, Mycapssa(r) (oral octreotide) was granted approval depending on a different mechanism. This technology is called Transient Permeation Enhancer (TPE(r)) technology and involves the use of Medium-Chain Fatty Acids (MCFAs) i.e. sodium caprylate (C8) and sodium caprate (C10) .

These MCFAs are classical PEs that work in the small intestine mostly only. Their mechanism, as opposed to SNAC, is paracellsular. They are thought to interact briefly and transiently with and rearrange tight junction proteins (such as ZO-1), to temporarily open the paracellular pathway so that the drug can pass through the cells.

The observation that the only two commercially successful oral biologic preparations employ radically different and site-selective PE mechanisms is a critical observation. It illustrates the fact that there is no right mechanism. The success of SNAC, which is highly contingent on the particular agent it is being designed to enhance) indicates that the future of this field is with the design of "bespoke" excipients, wherein the PE mechanism is designed to be rationally specific to the chemical characteristics of the biologic and its site absorption.

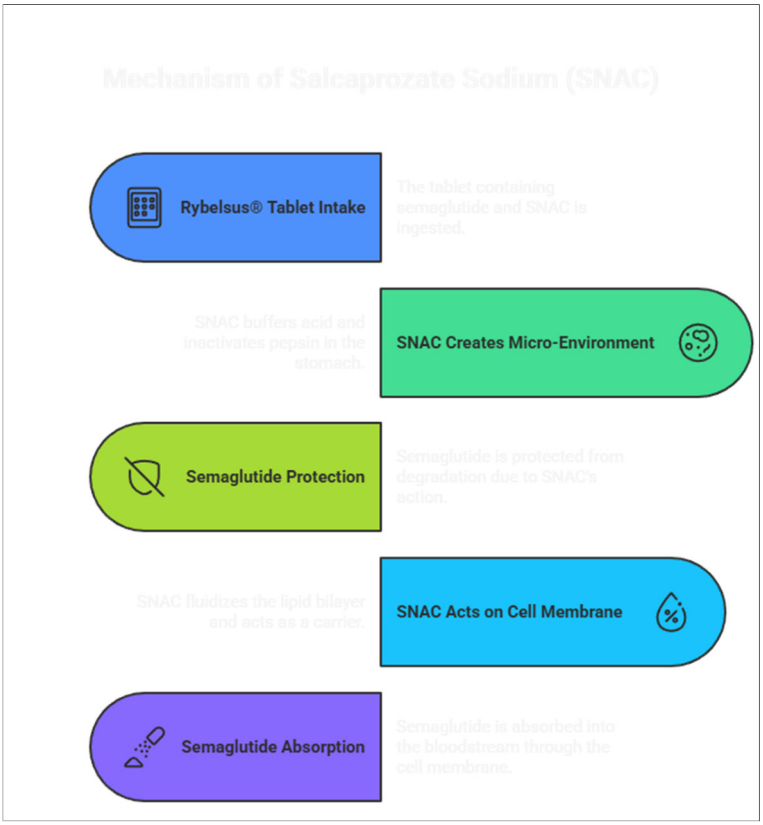

Figure 2. (A) The 2D chemical structure of Salcaprozate Sodium (SNAC) . (B) A diagram illustrating the proposed multi-modal mechanism of SNAC. After the tablet sediments in the stomach, SNAC provides (1) localized pH buffering to protect semaglutide from acid/pepsin degradation and (2) promotes transient, localized transcellular absorption by fluidizing the gastric cell membrane .

4. PHARMACEUTICAL STRATEGIES II: ADVANCED NANOCARRIER DELIVERY SYSTEMS

The second big paradigm shifts the focus of co-forming of the so called helper excipients to wrapping the biologic within a so called armored vehicle. Nanocarrier systems The nanocarrier systems include liposomes, polymeric nanoparticles, solid lipid nanoparticles (SLNs), and micelles, which are constructed to protect the payload and transport it across the GI barriers.

4.1 Safeguarding the Payload: The Armored Vehicle.

Encapsulation is primarily done to shield the biologic. The shell of the nanocarrier makes the payload (delicate protein or peptide) resistant to the harsh environment of the stomach as well as the cascade of enzyme degradation in the lumen, due to its physical barrier. An example is liposomes, which are very versatile, with an aqueous core (hydrophilic drugs, such as peptides) and a lipid bi-layer (hydrophobic drugs), rendering them capable of encapsulation of a great range of therapeutics.

4.2 Finding a Way through the Mucus: The Stick vs. Slip Conundrum.

After passing the lumen the nanocarrier must pass the mucus layer. This impediment shows the stick vs. slip paradox, as observed in Section 2, and nanocarrier designs have adapted in line with either of these approaches.

The Strategy of the "Stick" (Mucoadhesive Systems):

The purpose of this strategy is to stick to the mucus layer. It uses bioadhesive polymers, the most common of which is chitosan (cationic, natural polymer) and polyacrylic acid.

Mechanism These polymers establish non-covalent interactions (electrostatic, hydrogen) with the anionic mucin glycoproteins.

Goal: The objective is to adsorb the nanocarrier onto the intestinal wall, which increases the residence time of the nanocarrier in the location of absorption . This contact time elevates the local drug concentration gradient giving the drug more time to be released and absorbed.

The Strategy of Slip (Mucus-Penetrating Systems):

This plan is of the contrary: to slip through the mucus sieve, without any contact.

Mechanism: This needs a subcutaneous coating that is net-neutral and hydrophilic that avoids the sticking to mucin. This has been conventionally done through PEGylation (a stealth polymer) .

A better "Slip": More improved and efficient is the application of zwitterionic coatings. Zwitterionic polymers (e.g., including betaine side chains) are created to replicate the surface of some viruses that have been known to move through mucus without hindrance. The density of their charges is hydrophilic and net-neutral, preventing mucin adhesion on these surfaces so that the surface can readily diffuse across the mucus barrier.

4.3 Aiming at the Epithelium: Violating the Wall.

Once the nanocarrier has penetrated through the mucus, it will have to cross the mucus epithelial barrier. In this case, several specific strategies are used.

Charge-Mediated Uptake: Cationic nanoparticles (such as the chitosan stick particles) that are attached to the mucus can also deal with the negatively charged cell membrane of the epithelial cells and result in uptake through endocytosis.

Ligand-Mediated Uptake (Active Targeting): This is a more advanced method. Certain ligands (e.g. lectins, transferrin, Vitamin B12) are conjugated to the surface of the nanocarrier. Such ligands are selected to stimulate particular and endogenous receptors on enterocyte or M-cell (special immune cells in the gut) surfaces. This binding takes over the normal transport pathways of the cell, inducing a very efficient receptor based endocytosis.

Emergence of zwitterionic nanocarriers to deliver insulin orally has been a genius way out of the paradox of conflicting needs. This one design platform only executes both functions consecutively; the slip and the stick:

"Slip" (Mucus): To begin with, the zwitterionic (betaine-like) surface serves as a stealth coat. It is net-neutral and mimetic of viruses, and can therefore slide easily through the mucus layer at high speed, escaping the adhesion and clearance that would capture a cationic particle .

Stick (Epithelium): When this zwitterionic structure gets to the surface of the epithelial cell, it is considered a substrate. It has high affinity to endogenous cell surface transporters, PEPT1 or PAT1 (Proton-assisted Amino acid Transporter 1) .

Such a master key design is a pinnacle of rational design. One surface chemistry avoids the mucus barrier (or slip) and then, when it reaches the cell, invades a particular transporter to penetrate the epithelial barrier (or stick). This approach reaches a resolution of the main dilemma of nanocarrier design: it bypasses the guard (mucus) and then employs a key to enter a certain door (transporter).

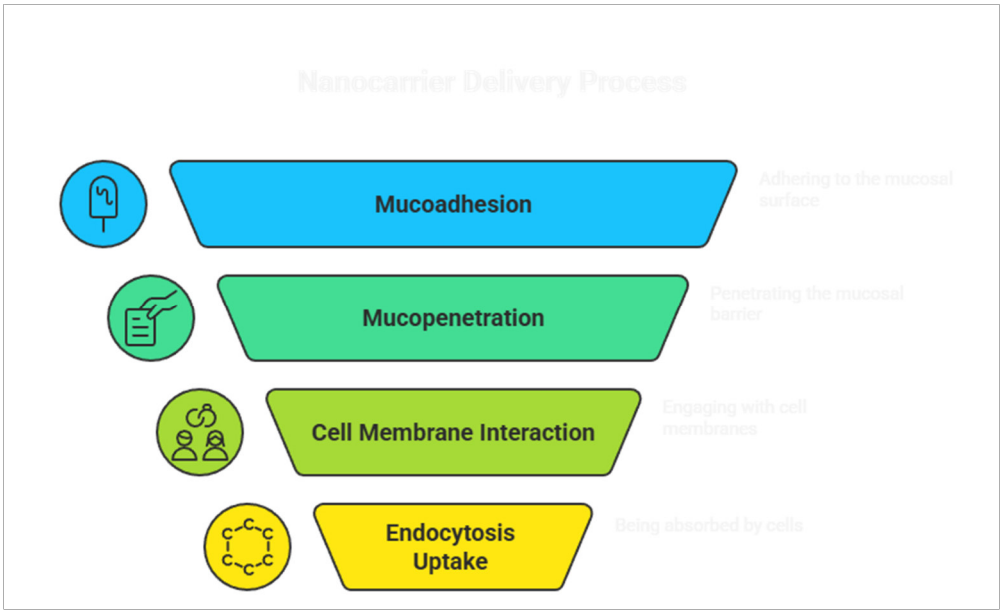

Figure 3. A flowchart illustrating the decision tree for nanocarrier design, which diverges based on the "stick vs. slip" approach to the mucus barrier. The "stick" strategy (left) uses mucoadhesion to prolong residence time. The "slip" strategy (right) evades mucus, requiring a subsequent epithelial targeting mechanism, such as receptor-mediated endocytosis (2a) or, in the case of zwitterionic particles, hijacking endogenous transporters (2b).

5. PHARMACEUTICAL STRATEGIES III: INGESTIBLE MECHANICAL DEVICES

The most radical paradigm of oral biologic delivery is one that goes beyond chemistry and formulation to the mechanical engineering science. In case GI barriers cannot be easily fooled, then it is possible to circumnavigate them. These digestible gadgets are programmed to contemplate the physiological obstacles and deliver the drug payload to or across the intestinal wall by physically pushing it.

The Microneedle Capsules (The "Pill-jection")

5.1 Microneedle Capsules:

The Microneedle Capsule is a sterile plastic device that mimics the tip of a pen, measuring about 15mm long, 8mm wide, and 8mm in depth.<|human|>5.1 Microneedle Capsules (The Pill-jection) Microneedle Capsules (The Pill-jection): This device is an instrument resembling the end of a pen; it has a

It is a pill-jection, an ingestible pill which, after swallowing, releases a set of small, drug-tipped microneedles to inject the contents directly into the GI tissue. Since the intestinal wall lacks pain receptors, this injection is painless.

One of the most prominent ones is the Luminal Unfolding Microneedle Injector (LUMI) .

Mechanism: LUMI is in a standard sized and enteric coated capsule. This coating is dissolved in the small intestine and the device is released. An elastomeric core is then used to unfold three arms by the LUMI in a rapid forceful manner. This active process has the added advantage of stretching the intestinal tissue and offers the motive force to drive patches of dissolving and drug-loaded microneedles through the tissue wall. The biologic (e.g., insulin) is then dissolved off of the microneedles and into the abundant vasculature of the intestine. The arms and core of the device are degradable which means they are passed to the GI tract safely.

5.2 Gastric Auto-Injectors

The other solution is a very advanced one wherein a swallowable, gastric auto-injector can be developed. A good example of this bio-inspired engineering is the Liquid-injecting Self-Orienting Millimeter-scale Applicator (L-SOMA).

Mechanism: L-SOMA is developed to provide a liquid preparation through injection into the stomach wall. Two major problems that its design addresses are:

Orientation: The device is based on the leopard tortoise and has high-curvature top and low center of mass. This enables it to self-right or self-orient within the stomach within less than one second, which means the needles of the injections are always directed at the wall of the tissues but not at the empty lumen.

Actuation: This is a hydration-based plug inside the device that is dissolved in the stomach fluid. This plug fires a compelled spring, which activates and pushes a needle deep into the submucosa of the gastric lining delivering the liquid drug cargo.

Efficacy: It is reported to have demonstrated impressive pre-clinical results, administering 4mg doses of adalimumab (monoclonal antibody), at up to 80 percent absolute bioavailability in swine, which is equivalent to a normal subcutaneous injection.

5.3 Mucoadhesive Patches

A milder mechanical treatment method is the "intestinal patch" . This device comprises an enteric-coated capsule which harbors a multi-layered and mucoadhesive film.

Mechanism: The patch is adhesive when digitalized and discharged in the intestine attaching to the intestine wall. The patch is created to have a protective and impermeable backing layer to ensure that a drug does not leak into lumen. This generates a steep concentration gradient and pushes unidirectional drug movement across the film into the tissue of the epithelial cell to which the film is fixed. This idea has been studied in case of peptides such as insulin and exenatide.

The location where to put these devices-stomach or intestine- is a very important engineering compromise.

Stomach (L-SOMA): The reason why this target is selected is because it is fast and safe. It administers the medication within minutes that avoids the 1-4 hour gastrointestinal emptying interval. Importantly, the thickness of the stomach wall is 4-6 mm, and it offers an enormous safety margin against a perforation (versus the small intestine wall, which is thin (0.1-2 mm).

Intestine (LUMI, Patch): An ideal target because of the large surface area and high blood flow of the small intestine which is the natural location in the body made to absorb.

This brings out an inherent predicament in designing the device in that it has to make a decision between the Speed and Safety of the stomach or the high Absorptive Capacity of the intestine.

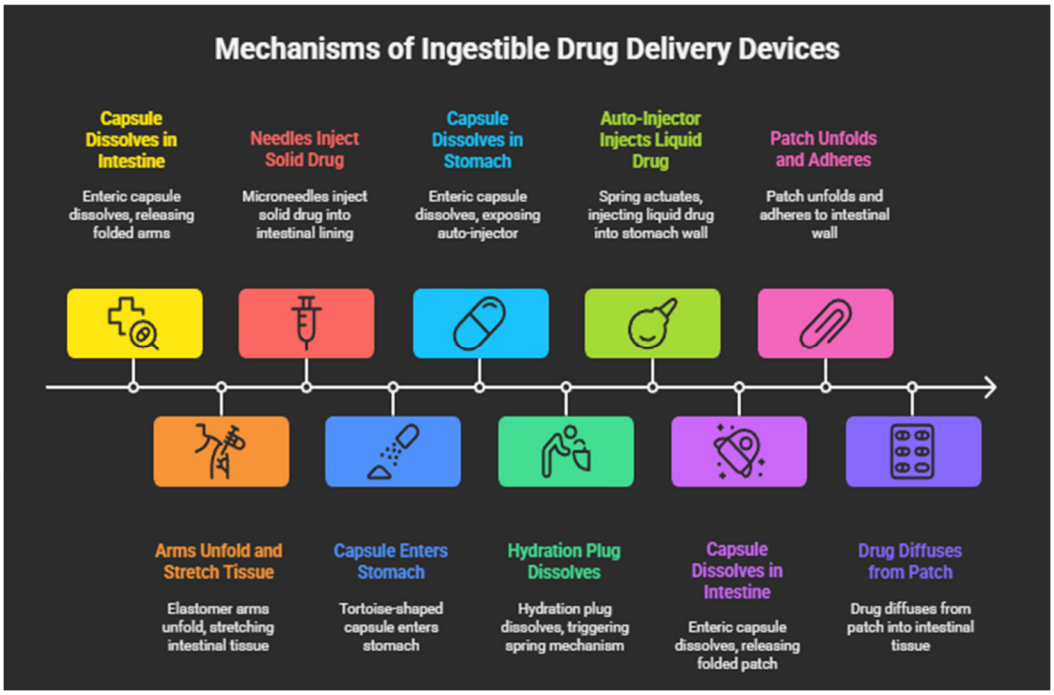

Figure 4. A comparative schematic of the three major ingestible device strategies. (A) The LUMI, which unfolds in the intestine to inject solid microneedles. (B) The L-SOMA, which self-orients in the stomach to perform a liquid injection . (C) The Mucoadhesive Patch, which sticks to the intestinal wall to provide unidirectional drug diffusion.

Table 1. Overview of Key Oral Biologic Delivery Strategies and Platforms

Strategy Category	Specific Example	Proposed Mechanism of Action	Key Barrier(s) Overcome	Payload / Status
xcipient (PE)	**SNAC (Rybelsus®)**	Transcellular transport; Local pH buffering; Gastric membrane fluidization.	Enzymatic (Stomach); Epithelial (Transcellular).	Semaglutide (Clinically Approved)
Excipient (PE)	**C8/C10 (Mycapssa®)**	Paracellular transport; Transient modulation of Tight Junctions (TJs).	Epithelial (Paracellular).	Octreotide (Clinically Approved)
Nanocarrier (Mucoadhesive)	**Cationic (Chitosan) NPs**	Electrostatic adhesion to mucus; Prolongs residence time; Endocytosis.	Residence Time; Enzymatic (Protection); Epithelial.	Pre-clinical (Insulin)
Nanocarrier (Mucopenetrating)	**Zwitterionic Micelles**	"Slip" (mucus penetration) + "Stick" (transporter uptake via PEPT1/PAT1).	Mucus; Enzymatic (Protection); Epithelial (Transporter).	Pre-clinical (Insulin)
Ingestible Device (Microneedle)	**LUMI**	Mechanical unfolding; Injection of dissolvable microneedles into intestinal wall.	*Bypasses* all barriers (Mucus, Epithelial).	Pre-clinical (Insulin)
Ingestible Device (Auto-Injector)	**L-SOMA**	Mechanical self-orientation; Spring-actuated injection of *liquid* into gastric submucosa.	*Bypasses* all barriers (Acid, Mucus, Epithelial).	Pre-clinical (Adalimumab, 80% BA)

6. PHARMACOLOGICAL CHALLENGES AND THE PATH TO CLINICAL REALITY

It is not enough to demonstrate an effective mechanism of delivery in vitro or in an animal model. Pharmacological hurdles lie on the way of clinical reality. A strategy may be found to work but must be shown to be effective, consistent and most importantly safe to be used by humans chronically.

6.1 Bioavailability and Variability Mystery.

The ultimate goal of any oral administration is the attainment of therapeutic bioavailability. This has been the impassable mountain over decades. The figures are still small by conventional standards even with modern PEs, the absolute bioavailability of oral semaglutide (Rybelsus (r)) is about 1%).

Bioavailability is however, entangled with a more challenging issue: variability. GI tract is a complicated and complex environment. Performance of formulations can be significantly altered by food, patient to patient variation of gastric emptying time, and local pH changes. Clinical failure is in part caused by high inter- and intra-patient variability, which can render the process of dosing erratic and hazardous.

Rybelsus (r) did not succeed: when a chronic medication of long half-life (the half-life of semaglutide is about 1 week to meaning that it is chronic) high bioavailability is not required. The half-life is long and is therefore

a buffer that levels the peaks and troughs due to variability in daily dosing and a low-but-consistent dose can be therapeutic. Consistency plays more significance in this model than high bioavailability.

In their turn, the device-based strategies demonstrate that high bioavailability can be created mechanically. The 80% BA of the L-SOMA with an antibody payload demonstrates that, bypassing the barriers completely, it is possible to make an oral capsule as efficient as an injection one.

6.2 The Safety Question: What about the Safety of 'Leaky'?

Long-term toxicological safety is the most acute pharmacological issue, specifically of PE-based strategies. PEs such as C8 and C10 act by temporarily breaking the intestinal barrier purposely and temporarily. This brings out two essential issues:

Is the interference really short-lived and reversible, or can there be some permanent damage with the continuous use?

Is there a breach of the "leaky" gut barrier permitting the co-absorption of the "bystander" agents-pathogens, endotoxins (LPS), or dietary antigens-that may cause inflammation, sepsis, or autoimmune diseases?.

These issues have in the past constrained the clinical translation of PEs. There is however a growing body of evidence that indicates that the gut epithelium is exceptionally hardy.

Reversibility: It seems that the damage is temporary. The laboratory experiments of C10 on Ussing chambers and in situ rat models indicate that although the perturbation of the membranes takes place, full histological recovery is observed within 30-60 minutes. There was a human study that demonstrated that intra-jejunal administration of C10 only enhanced paracellsular permeability less than 40 minutes only.

Chronic Dosing: A 2022 clinical trial of the chronic (1-month) daily oral of PEs in mice reported them to be safe and effective. The researchers determined that there was no permanent impairment of intestinal barrier functioning in repeated dosing.

The SNAC Safety Profile: The most interesting evidence is the clinical trials of Rybelsus(r). SNAC would not cause any serious effects in a long-term (9-month) animal study. Importantly, during Phase III human trial, the major GI side effects (e.g., nausea) were also similar to the injectable form of semaglutide. This has a strong implication that the cause of the side effects is the pharmacological action of the drug (semaglutide) and not the toxicological action of the enhancer (SNAC): this is a valuable validation of the safety of the excipient.

6.3 Immunogenicity

The last and, possibly, the most complicated task is immunogenicity. The gut is not merely a digestive organ but it is the largest immune organ in the body. Tolerance is usually produced as a result of oral administration of an antigen (such as a food protein). Nevertheless, the paradigm of the leaky gut of PEs forms a pharmacological paradox. We could be violating this oral tolerance by the co-administration of the biologic with an adjuvant (the PE), which interferes with the barrier.

The ideal recipe of creating anti-drug antibodies (ADAs) would be exposing a large protein therapeutic, when in a state of PE-induced inflammation, directly to the gut-associated lymphoid tissue (GALT) (Lila 2). The normal formation of ADAs may counteract the action of the drug, decrease its activity, or lead to severe adverse immunological reactions. Although the acute studies are encouraging, it is not well known as to the long-term immunological effects of repeatedly and deliberately breaching the gut barrier by way of chronic therapy, and this is a critical area that future studies can focus on.

7. CONCLUSION AND FUTURE OUTLOOK

It is not enough to demonstrate an effective mechanism of delivery in vitro or in an animal model. Pharmacological hurdles lie on the way of clinical reality. A strategy may be found to work but must be shown to be effective, consistent and most importantly safe to be used by humans chronically.

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Is there a breach of the "leaky" gut barrier permitting the co-absorption of the "bystander" agents-pathogens, endotoxins (LPS), or dietary antigens-that may cause inflammation, sepsis, or autoimmune diseases?.

These issues have in the past constrained the clinical translation of PEs. There is however a growing body of evidence that indicates that the gut epithelium is exceptionally hardy.

Reversibility: It seems that the damage is temporary. The laboratory experiments of C10 on Ussing chambers and in situ rat models indicate that although the perturbation of the membranes takes place, full histological recovery is observed within 30-60 minutes. There was a human study that demonstrated that intra-jejunal administration of C10 only enhanced paracellsular permeability less than 40 minutes only.

Chronic Dosing: A 2022 clinical trial of the chronic (1-month) daily oral of PEs in mice reported them to be safe and effective. The researchers determined that there was no permanent impairment of intestinal barrier functioning in repeated dosing.

The SNAC Safety Profile: The most interesting evidence is the clinical trials of Rybelsus(r). SNAC would not cause any serious effects in a long-term (9-month) animal study. Importantly, during Phase III human trial, the major GI side effects (e.g., nausea) were also similar to the injectable form of semaglutide. This has a strong implication that the cause of the side effects is the pharmacological action of the drug (semaglutide) and not the toxicological action of the enhancer (SNAC): this is a valuable validation of the safety of the excipient.

Immunogenicity

The last and, possibly, the most complicated task is immunogenicity. The gut is not merely a digestive organ but it is the largest immune organ in the body. Tolerance is usually produced as a result of oral administration of an antigen (such as a food protein). Nevertheless, the paradigm of the leaky gut of PEs forms a pharmacological paradox. We could be violating this oral tolerance by the co-administration of the biologic with an adjuvant (the PE), which interferes with the barrier.

The ideal recipe of creating anti-drug antibodies (ADAs) would be exposing a large protein therapeutic, when in a state of PE-induced inflammation, directly to the gut-associated lymphoid tissue (GALT) (Lila 2). The normal formation of ADAs may counteract the action of the drug, decrease its activity, or lead to severe adverse immunological reactions. Although the acute studies are encouraging, it is not well known as to the long-term immunological effects of repeatedly and deliberately breaching the gut barrier by way of chronic therapy, and this is a critical area that future studies can focus on.

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