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Oral Delivery of Monoclonal Antibodies: Challenges, Emerging Strategies, and Future Perspectives: A Review

Ashti M.H. Saeed[1], Maryam Alaayedi[2], Zahraa M. K. Alhendawi[2], Mayssam Hussein Mohammed Ali[1], Tiba Salah Mahdi[1] and Aqeel Abdulridha Khudhair[1]

[1]Department of Pharmaceutics, College of Pharmacy/University of Mustansiriyah, Baghdad, Iraq

[2]Department of Pharmaceutics, College of Pharmacy, Kerbala University, Karbala, Iraq

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Abstract

Monoclonal antibodies (mAbs) have changed modern medicine by making it possible to treat complicated diseases with specific and selected drugs. But giving these treatments by mouth is still quite hard. In the gastrointestinal tract, they have to deal with acidic pH, digestive enzymes, mucus barriers, and a limited ability to cross the intestinal wall, making them much less stable and less able to be absorbed. This review shows new solutions for these problems, such as liposomes and other nanoparticles as protective nanocarriers, mucoadhesive systems, enteric coatings, enzyme inhibitors, and permeability enhancers. It also shows new ideas like receptor-mediated transport, targeted diseases, and advanced oral delivery systems. New developments in antibody engineering and artificial intelligence are making it possible to make oral formulations that are more stable and selective. Problems that also limit the use of mAbs such as safety, cost, and consistency, but the quick development in this area shows that oral mAbs could one day be an easier option for patients to use compared to injections.

التوصيل الفموي للأجسام المضادة وحيدة النسيلة: التحديات، الاستراتيجيات الناشئة، والآفاق المستقبلية – مراجعة علمية

أشتي محمد حسين سعيد، مريم الأيادي، زهراء محمد كاظم الهنداوي، ميسم حسين محمد علي، طيبة صلاح مهدي، وعقيل عبد الرضا خضير

الملخّص

لقد أحدثت الأجسام المضادة وحيدة النسيلة (Monoclonal Antibodies, mAbs) نقلة نوعية في الطب الحديث، إذ أتاحت علاج أمراض معقّدة باستخدام علاجات نوعية وانتقائية عالية. إلا أن إعطاء هذه العلاجات عن طريق الفم لا يزال يشكّل تحديًا كبيرًا. ففي الجهاز الهضمي، تواجه هذه الأجسام المضادة بيئة ذات درجة حموضة عالية، وإنزيمات هاضمة، وحواجز مخاطية، إضافة إلى محدودية قدرتها على العبور عبر جدار الأمعاء، مما يؤدي إلى انخفاض كبير في ثباتها وقدرتها على الامتصاص. تستعرض هذه المراجعة عددًا من الحلول الحديثة للتغلب على هذه التحديات، مثل استخدام الليبوسومات والجسيمات النانوية الأخرى كحوامل نانوية واقية، والأنظمة اللاصقة للمخاط، والتغليف المعوي، ومثبطات الإنزيمات، ومحسّنات النفاذية. كما تسلّط الضوء على استراتيجيات مبتكرة تشمل النقل المعتمد على المستقبلات، والاستهداف الدوائي الموجّه، وأنظمة التوصيل الفموي المتقدمة. كذلك، تسهم التطورات الحديثة في هندسة الأجسام المضادة وتطبيقات الذكاء الاصطناعي في تصميم صيغ فموية أكثر ثباتًا وانتقائية. وعلى الرغم من استمرار وجود تحديات تحدّ من الاستخدام الواسع للأجسام المضادة وحيدة النسيلة، مثل قضايا السلامة والكلفة وضمان ثبات الجودة، فإن التطور السريع في هذا المجال يشير إلى أن التوصيل الفموي لهذه العلاجات قد يصبح في المستقبل خيارًا أكثر سهولة وراحة للمرضى مقارنةً بالإعطاء عن طريق الحقن.

1. Introduction

As envisaged, monoclonal antibodies (mAbs) have revolutionized contemporary medicine by providing a kind of specific and efficacious medical intervention against numerous health problems that include cancer, autoimmune diseases, cardiovascular diseases, allergies, osteoporosis, and even migraines. Outside of therapies, mAbs are used as critical reagents in organ transplant compatibility and blood typing and are key components in diagnostic assays for conditions such as pregnancy, ovulation, and infectious diseases. They are also essential components of public health systems used to screen for pathogens, including HIV, influenza, and the foodborne bacterium Salmonella (Tashima, 2021).

Because mAbs aren't very stable and don't get through the GI tract very well, the only ways to deliver them are by IV and SC. But these methods have disadvantages, such as injection-related discomfort, a higher risk of infection, and lower adherence, especially for chronic illnesses that need to be taken many times. Oral delivery is still the most popular method since it's easy to use, non-invasive, and makes patients more inclined to follow the instructions (Abramson et al., 2022). However, it is still very awkward to give mAbs by mouth. Their structures are intricate and weak as well as the acids and enzymes in the stomach and intestines can break them down. Besides, they have a high molecular weight and hydrophilic nature, which makes it challenging for them to passively diffuse across the intestinal barrier. Nanocarriers, mucoadhesive systems, and receptor-mediated transport are some other interesting ways to deliver drugs, although they often have issues with drug-loading capacity, bioavailability, and delayed pharmacokinetics compared to parenteral routes. To sum up, this review explores the major physiological and biochemical barriers to oral mAb delivery, assesses current and innovative strategies to overcome them, and provides insight into the future directions of this advancing field (Yadav, 2017; Yadav et al., 2016).

1.1. Biological and Structural Barriers to Oral Delivery of mAbs

There are a lot of biological and structural barriers in the GI system that make mAbs less effective when they are given by mouth (as shown in Fig.1). One important difficulty is that the enzymes break them down; for example, in the stomach, low pH and pepsin help break down proteins. Some of the enzymes that break peptide bonds even more in the small intestine are trypsin, chymotrypsin, and elastase. This breaks proteins down into smaller parts and amino acids. The colon possesses a lot of bacteria (10^{11}–10^{12} CFU/ml) that break down drugs through enzymatic activities, which is more than any other area of the body can handle (Baral & Choi, 2025; Drucker, 2020; Gelli et al., 2025). Besides, Peptide and protein treatments (PPs) have a lot of physiochemical features that make it challenging for oral drug delivery systems to activate. PPs are very big, hydrophilic, have limited membrane permeability, and tend to break down by enzymes. These characteristics have an effect on encapsulation, how easily it is absorbed, and how stable it is. They can also be denatured, oxidised, aggregated, or hydrolysed during formulation, manufacturing, and storage since their structures are very complex. Other properties that can make them less stable are pH, temperature, agitation, ionic strength, and interaction with surfactants or metal ions (X. Chen et al., 2025; Gelli et al., 2025).

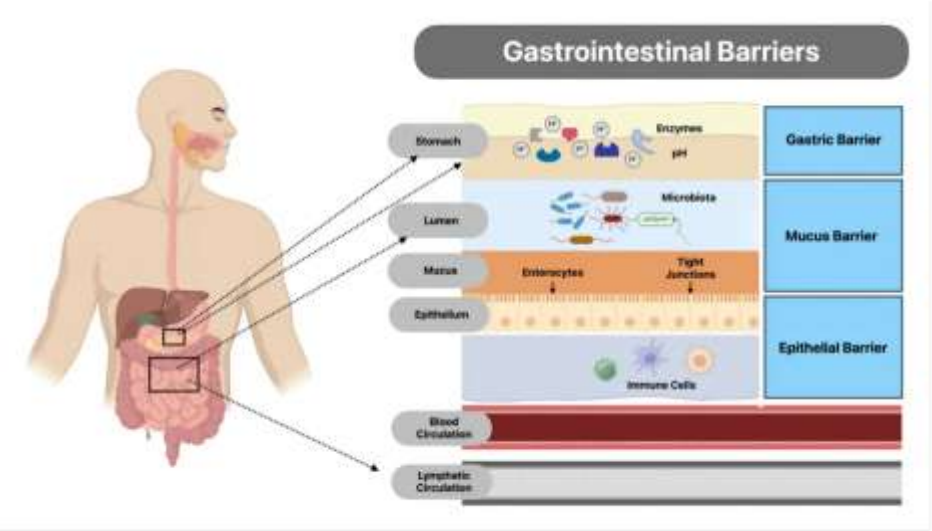

Figure1:Gastrointestinal barriers affecting oral drug delivery. Schematic illustration of the major physiological barriers encountered by orally administered therapeutics within the gastrointestinal tract. These include the gastric barrier (acidic pH and digestive enzymes), the mucus barrier with resident microbiota, and the epithelial barrier composed of enterocytes and tight junctions. Additional immune components beneath the epithelium further influence drug transport before entry into the systemic circulation via blood and lymphatic pathways.

1.2. Permeability and Physicochemical Properties

Because their molecules are so large, PPs have a hard difficulty penetrating through membranes. Small drug molecules (less than 500 Da) can usually penetrate the GI membranes by passive diffusion, whereas bigger macromolecules (1–100 kDa) have a lot of problems doing so. Because PPs are hydrophilic (logP < 0), it is considerably harder for them to interact with lipid bilayers. This is because they have to get through hydration shells before they can get into the membranes of cells. So, passive absorption is quite minimal, and most of the time, uptake comes by active transport or endocytosis. One problem with endocytosis is endosomal entrapment, which can lead to lysosomal destruction. The charge on the surface of PPs, which is controlled by the pH of their environment and the amino acids they are made of, also affects their permeability. Mostly, molecules that don't have a charge can move across membranes more easily than those that do. The solubility of PPs also is fluctuated with pH; at the isoelectric point (pI), they become zwitterions and don't move through membranes very well. This shows that electrostatic characteristics are more significant than hydrophobicity for absorption in the mouth (Adhikari & Pokhrel, 2025). PPs can also break down under physiological stress or when they are in systemic circulation. Moreover, Deamination, isomerisation, or post-translational changes might make their chemicals unstable, which can change surface charges and make undesired variations. These problems need to be fixed when designing oral formulations (Beach et al., 2024; G. Zheng et al., 2025).

1.3. pH and Enzymatic Barriers

The pH levels in the GI tract affect how well PPs stay stable and affect on their solubility. Enzymes in the stomach can easily change the shape of PPs and inactivate them. The pH can be anything from 1.0 to 2.0. In the duodenum, jejunum, and ileum, the breakdown of enzymes slows down when the pH rises. The colon, on the other hand, stays the same. Nevertheless, PPs are usually only stable in a small pH range that is close to their pH; changes in pH make them more hydrophilic and less able to go through membranes (Liang et al., 2020; Liu et al., 2017; Tong et al., 2020). Pepsin is a protease that breaks down proteins in the stomach. It operates best at pH 2–3 and becomes inactive above pH 5. In contrast, when the pH is higher, trypsin and chymotrypsin, which are enzymes in the intestines, work optimally. Changes in nutrition, food, diseases like cancer or inflammatory bowel disease, and more can all make the pH environment even less stable, which makes it harder for PPs to be absorbed and stay steady when taken by mouth (G. Zheng et al., 2025).

1.4. Enzymatic Barrier

Proteolytic enzymes make given PPs via mouth very challenging. Food has been broken down by pepsin, trypsin and chymotrypsin and by the microbial enzymes in the stomach, the pancreas, and the colon, respectively. Pepsin breaks proteins down into smaller fragments in the stomach, which makes it easier for subsequent enzymatic degradation. Enzymes that are close to the brush border of the intestinal lining can help make digestion and absorption more effective. In the stomach, only peptides that stay stable in the acidic environment and aren't broken down by pepsin can be absorbed. In the small intestine, more enzymes—like serine proteases and carboxypeptidases—continue breaking down PPs. For example, insulin is quickly broken down by trypsin and chymotrypsin, usually in less than an hour when conditions are normal (G. Chen et al., 2022; Tong et al., 2020). Besides luminal and brush-border enzymes, cytosolic enzymes within enterocytes also degrade PPs. Lysozymes, for instance, affect lipophilic PPs uptake through transcellular mechanisms. Microbial enzymes break down PPs into small fragments or amino acids, typically rendering them therapeutically inactive. Awareness of these pathways is essential to improving oral bioavailability (G. Chen et al., 2022).

1.5. Epithelial Barrier

Although the intestinal epithelium consists of a single cell layer, it forms a regulated interface composed of tight junctions and transmembrane proteins like occludin and claudins. The limited permeability of this barrier restricts the entry of large, hydrophilic PPs, which cannot pass through the lipid bilayer or narrow paracellular spaces (3–10 Å). The paracellular route represents less than 1% of the mucosal surface and is will not work for large molecules without transient disruption of tight junctions. Strategies such as penetration enhancers have been proposed to enhance this route by temporarily loosening junctional integrity (Puri, Loomis, Smith, Lee, Yavlovich, & Heldman, 2009; Puri, Loomis, Smith, Lee, Yavlovich, Heldman, et al., 2009).

1.6. Mucus Barrier

There are two layers of mucus in the GI tract: a hard layer that is attached to the epithelium and a loose layer undergoing constant renewal. This gel-like barrier is full of mucins and glycoproteins. Mucus keeps pathogens and macromolecules like PPs from moving about. It is a sticky covering that keeps the inside of the digestive tract safe. Mucins, which are proteins, make up most of it. They are cross-linked by disulfide bonds forming a flexible net-like shape. This structure can slow down or stop medications from moving by either trapping them or keeping them from squeezing through its tiny pores, which are just approximately 0.2 micrometers wide. Besides, molecules that are smaller or made for a specific purpose have a better chance of getting through. Peptides that are bigger than 6.5 kDa have a hard time getting through, and those that are bigger than 12.4 kDa frequently failed to reach [5]. On the other side, the pH level of mucus also changes depending on where it is in the gut. The pH is quite acidic (about 2.25) at the luminal surface, but it gets closer to neutral (about 7) at the epithelial interface. When the pH is close to the isoelectric point, these alterations can modify how peptides breakdown and travel through the mucus. Therefore, the drug delivery systems need to be made with a big attention to pH changes in mucus (Puri, Loomis, Smith, Lee, Yavlovich, & Heldman, 2009; Puri, Loomis, Smith, Lee, Yavlovich, Heldman, et al., 2009). In addition to the Sulfhydryl Barrier; some peptides have bisulfide bonds that help them keep their shape and can be inactivated by thiol-bisulfide exchange reactions in the GI tract. In the stomach, natural substances like glutathione and some nutrients from fruits and vegetables, such as N-acetyl cysteine and γ-glutamyl cysteine can break these bonds. When that happens, the peptide may stop working. (G. Zheng et al., 2025).

1.7. Current strategies to improve oral mAb delivery

1.7.1. Organic Nanoparticles

One of the main parts of organic nanoparticles is the liposomes (as shown in Fig.2) which can prevent the process that called hydrolysis in the acidic condition or by pepsin. Some liposomal antibodies are capable of releasing the antibodies in the areas which are extensively rich in the bile salts and thus released moieties does not get degraded in the presence of trypsin and chymotrypsin. GI tract thus gets immunized passively and gets prevented from the different viruses and bacteria (Adhikari & Pokhrel, 2025). Therefore, researchers are very interested in liposomes because they can protect macromolecules and help them get through the body more easily when taken by mouth. A new study showed that wrapping liposomes in polysaccharides from mulberry leaves made insulin far more stable and easier for the body to absorb through the gut. This method could also be used with mAB to stop them from being broken down by enzymes and make them easier for the intestines to absorb. Likewise, the study by Chen et al. showed that polysaccharide-caged liposomes have a prolonged release behaviour, which suggests that they could be useful for delivering mAbs. The modified liposomes only released around 40% of their contents in the first four hours, while uncoated liposomes released about 80%; this shows that the release profile was much longer. This kind of controlled release mechanism is good for oral mAb formulations because it may make them more stable and help them be absorbed better in the GI tract (X. Chen et al., 2025).

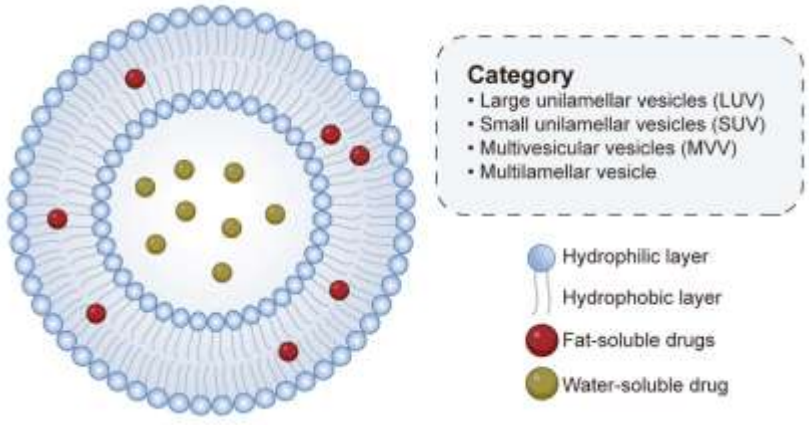

Figure1: ***Schematic illustration of liposomal drug delivery systems and their intestinal transport.*** **The diagram shows the structural organization of liposomes composed of hydrophilic outer surfaces and hydrophobic phospholipid bilayers, enabling the encapsulation of both water-soluble drugs (within the aqueous core) and fat-soluble drugs (within the lipid bilayer).** Different liposomal categories are illustrated, including large unilamellar vesicles (LUV), small unilamellar vesicles (SUV), multivesicular vesicles (MVV), and multilamellar vesicles. The lower panel demonstrates the proposed mechanism of liposome interaction with the intestinal epithelium, highlighting transport across the epithelial barrier and subsequent distribution via blood and lymphatic circulation, with potential modulation of immune cells in the gut environment.

Furthermore, one of the big problems with giving mAbs by mouth is that they can be broken down in the stomach and intestines. Even if some of the drug survives, it has poor systemic availability because the liver breaks it down during first-pass metabolism. Modified liposomal systems, like 2-monoacylglycerol (2-MAG), which are similar to liposomes, would be a smart way because they act like the body does when it absorbs dietary lipids. The enterocytes in the intestines take up these liposomes and turn them into chylomicrons. This allows them get into the intestines' lymphatic system; this lymphatic transport route goes around the liver's metabolism, which stops enzymes and the liver from breaking down the mAbs. This kind of scheme could make mAbs more powerful and more extensively distributed in the body, especially those that target immune cells located in lymphatic-rich tissues (G. Zheng et al., 2025).

1.7.2. Polymeric Nanoparticles

Polymeric nanoparticles, especially those based on PLGA and PLGA-PEG, have been employed to encapsulate anti-TNF-α mAbs, offering protection from enzymatic degradation and controlled release. A study demonstrated that PEGylated PLGA nanoparticles loaded with anti-TNF-α mAb significantly reduced TNF-α levels and improved histopathological scores in a murine colitis model. Interestingly, PEG2k-PLGA nanoparticles outperformed PEG5k-PLGA ones, highlighting the impact of PEG chain length on bioavailability and therapeutic effect (B. Zheng et al., 2024). Besides, the other method which is solid lipid nanoparticles (SLNs) with a particle size between 50 and 1000 nm, have a solid lipid matrix that makes the antibodies more stable and enhance their absorption in the intestines. These nanoparticles help against stomach degradation and make it easier for lymphatic uptake, which means they don't go through hepatic first-pass metabolism (Shrestha et al., 2022). A recent study made SLNs with tocilizumab, an IL-6 receptor-

targeting mAb, for oral use in COVID-19 treatment. This showed that the SLNs could be transported and had systemic bioavailability (Shrestha et al., 2022; B. Zheng et al., 2024).

1.7.3. Nano emulsions

They are an oil-in-water/water-in-oil dispersions with droplets that are only a few nanometres wide. They make protein drugs easier to dissolve and help them interact better with intestinal mucus. Studies have indicated that Nano emulsions can help transcellular and paracellular transport across intestinal epithelia. For example, they boosted the delivery of anti-TNF-α drugs in models of inflammatory bowel disease (Lei et al., 2023).

1.7.4. Mucoadhesive

Mucoadhesive drug delivery systems have become a viable way to make therapeutic substances more available in the mouth, especially macromolecules that would otherwise be unstable throughout the digestive tract. Mucoadhesive formulations can stay at the site of absorption longer by sticking to the mucus layer that covers the epithelial surfaces; this lets more medicine be absorbed and less exposure to enzymatic breakdown and first-pass metabolism. Researchers have studied these kinds of devices for small chemicals and peptides, but they could be very useful for delivering mAbs by mouth because they need to stay in contact with the mucosa for a long time and be protected from harsh GI conditions (by protects sensitive biologics from degrading enzymes and changing pH levels while they are moving through the gut lumen). Equally, many reviews support this idea by showing how mucoadhesive polymers can help drugs stay in the body longer and be absorbed better, which shows that they could be useful for creating oral mAb delivery methods (Alawdi & Solanki, 2021; Kali et al., 2024). Mucoadhesive drug delivery systems have a useful advantage because they allow medicine to be absorbed through mucosal areas such as buccal, sublingual, nasal and rectal pathways. This means the drug can enter the bloodstream without first being filtered or broken down by the liver. Since the medicine stays in place longer on the mucosal surface, it has more time to be absorbed effectively -making the treatment faster and sometimes more reliable. This feature is especially useful for macromolecular biologics like monoclonal antibodies which are usually unstable in the digestive system and go through a lot of liver metabolism when taken by mouth (Kali et al., 2024; Sharma et al., 2024; Vivek Kumar et al., 2014). Consequently, researchers have found that mucoadhesive formulations can get into and be absorbed better than regular oral dose forms. This method also lets medications be released in certain areas of the gastrointestinal tract, such the stomach or small intestine. At the same time, hence; protects sensitive biologics while they move through the tough environment in the gut. Moreover, specialized polymers like thiolated chitosan, PEGylated mucoadhesive, and pH-sensitive anionic copolymers (such Eudragit derivatives) have been used to make these systems even better. These materials make the formulation work superior with mucus, which helps it stay in place longer, travel deeper into the body, and absorb more of the medicine at the target spot. These polymers likewise function by either loosening the mesh of mucus for a short time or tightening the connections between epithelial cells. This helps the medicine persist at the target place and be taken up by receptors, like M-cells. Thiolation (via sulfhydryl groups), PEGylation, and pH-sensitive grafting are some of the alterations they make; all of these help biologics like mAbs get through the GI system more easily and protect them as they do so (Kumar et al., 2022; Sharma et al., 2024).

1.7.5. Enteric Coating

Enteric coatings are highly significant for monoclonal antibodies that are taken by mouth because they keep the dosage form from breaking down in the stomach and only breaking down in the small intestine. These polymer barriers are affected by pH. They are stable in the acidic stomach (pH 1–3) but break down in the higher intestine pH (~>6). This stops mAbs from breaking down too soon and being broken down by stomach enzymes. Clearly, when mAbs get to the gut, they can interact better with the absorptive epithelium and take part in mechanisms like neonatal Fc receptor (FcRn)-mediated transcytosis, which help them enter into the body. Enteric-coated nano- or microparticulate systems have been found to assist antibodies stay alive longer in the GI tract and be released successfully in the small intestine (Yamaguchi et al., 2022).

1.7.6. Enzyme Inhibitors

Proteolytic enzyme inhibitors are found in oral protein formulations. These inhibitors prohibit digestive enzymes from breaking down mAbs in the gut. These inhibitors stick to active enzyme sites in a certain way, either reversibly or irreversibly. They are protease inhibitors that come from amino acids, peptides, and polypeptides. Some of the most popular agents used are aprotinin (trypsin and chymotrypsin inhibitors), leupeptin (plasmin, trypsin, and papain inhibitors), soybean trypsin inhibitor, and chicken ovomucoid. Researchers have observed that adding these inhibitors to oral mAb administration methods considerably slows down the enzymatic breakdown. This means that biologics last longer and are better absorbed in the intestinal lumen than formulations that don't have protease inhibitors (Dan et al., 2020). Protease inhibitors are often integrated into advanced ways of taking medications by mouth, like nanoparticles and microspheres that are coated with enteric or polymer, to stop macromolecular drugs like monoclonal antibodies from breaking down in the stomach. The delivery carriers make sure that the medications are distributed in a controlled fashion at the right sites in the intestines (Lei et al., 2023). Additionally, this two-pronged strategy not only slows down the degradation of the drug, but it also helps the epithelial cells in the area absorb it better (Ibrahim et al., 2020). Some amino acid-based excipients, like arginine, histidine, and N-acetylcysteine, can stop enzymes from working and keep proteins stable in oral mAb formulations. By slowing down the activity of digestive proteases including trypsin, chymotrypsin, and pancreatic elastase, they assist mAbs preserve their shape as they go through the digestive system. When these excipients are incorporated into certain delivery systems, including enteric-coated capsules, polysaccharide films, or pH-triggered nanoparticles, they assist make a safe environment. This technique results in higher levels of intact antibodies in the lumen and better tissue uptake than formulations that don't employ these kinds of excipients. Besides, recent evaluations show that amino acid-based stabilisers are necessary for better ways to deliver proteins and peptides orally because they help get around problems that make them breakdown and make them more bioavailable (Ibrahim et al., 2020; Maher et al., 2019; Pangua et al., 2024).

1.8. Permeation Enhancers

1.8.1. Mechanism of Permeation Enhancers (Pes):

PEs can help macromolecules get into the body through the mouth through several mechanisms. First, they can temporarily disrupt the tight connections between epithelial cells, which makes the paracellular permeability higher and lets big molecules like mAbs get through the intestinal barrier. Second, certain enhancers work by increasing membrane fluidity, which makes it easier for substances to move across epithelial cells. Besides, certain PEs work by inhibiting proteolytic enzymes in the gastrointestinal (GI) tract, which slows down the breakdown of protein-based drugs by enzymes. These actions work together to get over the big physiological problems that come with giving biologics by mouth (Pangua et al., 2024; Twarog et al., 2019). Researchers have looked into a number of techniques to make macromolecules more permeable so that the intestines can better absorb big molecules like therapeutic proteins. For example, these enhancers affect membrane fluidity or make the connections between cells less tight. These are some of the most studied by the researchers to realise if they can make biologics, like as monoclonal antibodies, more bioavailable orally while keeping the mucosa safe (Ibrahim et al., 2020; Maher et al., 2019; Pangua et al., 2024; Twarog et al., 2019):

- **a)** Medium-chain fatty acids (MCFAs), such sodium caprate (C10), can reversibly open tight junctions so that paracellular transport can place.
- **b)** Bile salt derivatives, including sodium deoxycholate and other surfactants, that improve transcellular absorption by disrupting lipid membranes in a controlled fashion.
- **c)** Surfactants and solubilising agents like sodium dodecyl sulphate (SDS) and labrasol make membranes more permeable and help dissolve hydrophobic domains.
- **d)** Chelating agents like EDTA that stick to calcium ions to open tight junctions and make it easier for paracellular passage.
- **e)** Zonula occludens toxin (ZOT) and its synthetic forms change how tight junction proteins work to enhance mucosal permeability.
- **f)** SNAC (sodium N-[8-(2-hydroxybenzoyl) amino] caprylate) is a clinically tested enhancer that promote trancellular delivery by increasing membrane fluidity and protecting against enzymatic degradation. This makes it easier for drugs to get into cells.

1.9. Formulation Approaches of Pes:

1.9.1. Nanoparticle-Based Strategy for Oral Delivery of Mabs

Recent preclinical studies have shown that putting monoclonal antibodies inside nanoparticles can get through mucus and improve their oral bioavailability. One possible method is to use polyethylene glycol (PEG)-coated albumin-based nanoparticles that are mixed with permeability enhancers like sodium deoxycholate. Not only does this design make it easier to get through the mucus layer, but also makes it easier for the epithelium to absorb. This method has led to more than a 1000-fold improvement in oral bioavailability in experimental models (Maher et al., 2021).

1.9.2. Co-Localised Release

Early-stage clinical and preclinical studies have shown that the optimal co-localization of the permeation enhancer and the macromolecule at the intestinal epithelial surface is important to maximize the absorption. Traditional oral dosage forms may suffer from premature dilution of both components in the gastrointestinal fluid, resulting in limited bioavailability. Innovative delivery platforms—such as mucoadhesive hydrogels, bioadhesive matrices, and controlled-release nanocarriers—are currently being investigated to maintain a high local concentration of both the drug and enhancer at the mucosal interface, improving paracellular or transcellular uptake (McCartney et al., 2016).

1.9.3. Advanced Devices

Advanced oral delivery devices offer an innovative strategy to overcome gastrointestinal barriers (as mentioned figure1) without relying on chemical permeation enhancers. Robotic capsules and self-orienting gastric auto-injectors are technologies that are capable to mAbs directly across the mucosal layer by applying microneedles or pressure-based systems. Preclinical models have shown that these devices can achieve systemic bioavailability levels close to subcutaneous injections, so they are a viable option for the oral administration of biologics (Y. Zheng et al., 2018, 2019).

1.9.4. Clinical Translation and Limitation of Pes:

PEs have made it possible to give some peptides and proteins orally, though they can't be used on mAbs yet because they have a low and extremely variable bioavailability. Therefore, they can only be used on molecules with high potency and have a high level of safety margins. There are also worries regarding mucosal safety, especially the chance that undesirable substances, like bacterial endotoxins, could get through the gut barrier, since; repeated exposure could potentially cause local irritation or epithelial disruption. Only a few oral formulations with permeation enhancers have been approved for clinical use. This is because it is still hard to make sure that they work consistently, keep patients safe, and keep the formulation reproducible (McCartney et al., 2016).

1.9.5. Receptor Mediated Transcytosis

Receptor-mediated transcytosis (RMT) is a promising way to help distribute monoclonal antibodies orally. This route starts with antibodies or ligands attaching to membrane-bound receptors on intestinal epithelial cells. Then, endocytosis, intracellular trafficking, and exocytosis happen at the basolateral side. Simply, RMT is a process that is often studied for moving biologics across the blood-brain barrier through receptors like transferrin and insulin receptors. It has recently been interesting as a possible way to improve the absorption of therapeutic macromolecules in the intestines. Even though the physiological settings are different, the basic idea—using receptor specificity to direct nanoparticle or antibody-receptor complexes through epithelial cells via endocytosis and intracellular trafficking—can be used in the gastrointestinal tract. Studies using transferrin-modified nanoparticles have shown that protein drugs are more stable and can be absorbed better in the intestines. This suggests that RMT-based methods developed for delivering drugs to the central nervous system could help improve the oral delivery of monoclonal antibodies (Mantaj & Vllasaliu, 2020; Vllasaliu et al., 2018).

The neonatal Fc receptor (FcRn) is one of the most researched targets. It is very important in IgG homeostasis because it binds antibodies in endosomes at acidic pH and moves them intact across cell barriers. Using FcRn in the intestinal epithelium might make it possible for protected transport of therapeutic mAbs to go through cells and into the bloodstream. Some researchers have also suggested that other receptor systems, including the megalin-cubilin complex, may help the gut absorb IgG. However, their role in the small intestine is still being studied (Mantaj & Vllasaliu, 2020; Vllasaliu et al., 2018; Y. Zheng et al., 2019). Nanoparticles can be made to target certain receptors on intestinal cells that are involved in receptor-mediated transcytosis. This not only makes them more stable, but it also helps transcellular transport. M cells in Peyer's patches have a good endocytic activity and can be good places for nanoparticles to enter the body. By targeting these cells with delivery mechanisms, it may be possible to improve the transport of antigens across the intestinal epithelium and make orally given biologics more bioavailable (Zanjare, 2024). Recent improvements in oral biologic administration have led to the development of device-assisted techniques that avoid many of the issues that arise with classic chemical enhancers. Some of them are trans enteric robotic pills and other devices that may be swallowed. They have been proven to be able to deliver mAbs at levels of systemic exposure that are similar to those attained by parenteral methods. These approaches protect therapeutic antibodies from harsh circumstances in the stomach and help them go to the small intestine through receptor-mediated pathways. This makes gastrointestinal absorption more effective (Yamaguchi et al., 2022).

1.10. Challenges Remaining and Safety Concerns

1.10.1. Immunogenicity (Immune Reactions)

Therapeutic mAbs, especially ones given in non-traditional routes, have a significant chance of making anti-drug antibodies (ADAs), which could neutralize the therapy or induce allergic reactions. Even fully human or humanised mAbs can trigger immune responses if their structure or aggregation changes (Twarog et al., 2019).

1.10.2. Structural Instability In GIT

Antibodies are large and delicate proteins that break down easily in the acidic, enzyme-rich GI tract. Stomach acid, pepsin, trypsin, and chymotrypsin can change the structure of proteins, causing them to clump together, and lose function. This can happen unless they are protected by advanced formulations such enteric coatings, nanoparticles, or enzyme inhibitors (Ahmadi et al., 2024; Parola et al., 2018).

1.10.3. High Cost of Oral Mab Formulations

Making monoclonal antibodies is already highly expensive. Adding technology like nanoparticles, absorption enhancers, or novel delivery systems (such robotic capsules or microneedle pills) makes production and development costs even higher. This makes people worry about whether they can be sold and whether patients can access them (Parola et al., 2018).

1.10.4. Long-Term Safety of Absorption Enhancers

Oral mAb formulations sometimes have chemical permeation enhancers added to them to temporarily make the intestinal epithelium more permeable. These can include surfactants, bile salts, fatty acids (like sodium caprate or sodium deoxycholate), or small permeation-promoting molecules. Many of these enhancers appear

safe in the lab, but there are worries about how safe they will be after a long-term use. It could make the mucosal barrier weaker, disrupt tight junctions, and change how the local immune system works if you use it for a long time. For example, a 30-day study on mice that gave them daily doses of sodium caprate (C10), sodium deoxycholate (SDC), and 1-phenylpiperazine (PPZ) found that there was no permanent increase in intestinal permeability, no damage to the epithelium, and tight junction proteins returned to normal after wash-out (Scott Crowe et al., 2018).

1.11. Future Perspectives

1. Engineered Antibodies and New Molecular Designs

Recent progress in protein engineering has made it possible to create monoclonal antibodies that are easier for the body to take in orally, more stable in structure, and less likely to trigger an immune response. You can change the Fc or variable domains of these altered antibodies to make them more likely to pass through the intestines and less likely to be broken down by proteolytic enzymes. This makes them easier to use in the mouth. Changes like PEGylation, glycoengineering, and Fc fusion with stabilising moieties are all examples of these. These methods are the initial stage in making oral mAbs therapeutically effective (Zielińska et al., 2023).

2. Artificial Intelligence (AI) In Antibody And Formulation Design

Scientist can use AI and machine learning (ML) to look at the massive antibody sequence library in silico and predict how stable the structure will be, binding affinity, and how well it can be developed. These methods also can help to choose the best candidates for oral delivery that are resistant to protease as well as in making formulations by figuring out the ideal excipients and circumstances to keep macromolecules stable in the stomach. This combination of computer modelling and real-world testing speeds up lead optimisation and could save the time it takes to make oral mAb therapeutics (Scott Crowe et al., 2018; Zielińska et al., 2023).

3. Disease-Specific Targeting (IBD Therapy by Oral mAbs)

Site-specific therapy is expected to play an important role in the future of oral monoclonal antibody delivery, especially for gastrointestinal conditions such as inflammatory bowel disease (IBD). One promising example is V565, a domain antibody that has shown potential in early-stage IBD models and is currently being studied by researchers. It was made to stay stable in the mouth and not break down in the stomach. When given orally to mice with colitis, it caused high levels of TNF-α neutralisation in the gut, especially in the intestinal tissues, and very little exposure to the rest of the body. This suggests that it was able to effectively control inflammation in the gut and was safer than injectable adalimumab (Iida, 2019; Parola et al., 2018; Scott Crowe et al., 2018).

2. Conclusion

Enzymatic degradation, poor permeability, and low bioavailability are problems that are still make it impossible to deliver monoclonal antibodies via mouth. Even though a lot of research has been done, no oral mAb product has been used in clinical practice on a regular basis yet. But the fast progress in molecular engineering, nanocarrier systems, and site-specific targeting techniques makes it seem more and more likely that this will happen. Using AI to design antibodies, along with disease-focused delivery approaches—e.g., for IBD—shows that treatments are becoming more precise and easier for patients. Although there is still a long way to go before oral mAbs are used in real life, the progress so far points to a promising and exciting future.

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