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Review Article

Hydrogel-based oral delivery of biologics: breaking the barrier

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ABSTRACT

Oral delivery of biologics offers unmatched advantages in patient compliance and therapeutic convenience but faces formidable challenges due to enzymatic degradation, poor epithelial permeability, and first-pass metabolism. Hydrogel-based delivery systems have emerged as a promising solution, leveraging their biocompatibility, tunable structures, and responsiveness to gastrointestinal stimuli to protect fragile biologic drugs and enhance their systemic bioavailability. This review explores the physiological barriers hindering oral biologic delivery and discusses advanced hydrogel design strategies, including mucoadhesion, pH-sensitive release, enzyme-responsive behavior, and nanoparticle embedding. Recent innovations such as microbiome-responsive hydrogels and artificial intelligence-assisted formulation design are reshaping the landscape, enabling smart, targeted, and patient-specific therapies. In vivo studies demonstrate significant improvements in pharmacokinetics, absorption, and therapeutic efficacy, while early clinical trials suggest a promising translational potential. However, regulatory, stability, and large-scale manufacturing challenges persist, necessitating further multidisciplinary collaboration. By overcoming these barriers, hydrogel-based oral delivery platforms are poised to revolutionize the administration of proteins, peptides, nucleic acids, and antibodies, offering a future where non-invasive, precision-targeted biologic therapies become the standard of care.

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Introduction

Oral administration remains the most preferred route for drug delivery due to its simplicity, non-invasiveness, and enhanced patient adherence compared to injectable therapies [1].

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For chronic diseases requiring long-term treatment, such as diabetes or autoimmune disorders, oral drug delivery significantly improves patients' quality of life by reducing hospital visits and procedural anxiety [2]. However, despite these advantages, the effective oral delivery of biologics remains highly challenging. Biologic drugs, including proteins, peptides, antibodies, and nucleic acids, are large, complex molecules that face multiple physiological barriers when administered orally. The gastrointestinal (GI) environment presents harsh acidic pH conditions, digestive enzymes (e.g., proteases, lipases), and a thick mucus layer, all contributing to rapid degradation of biologics before they reach the systemic circulation [2,3].

Moreover, the epithelial barriers of the intestines are selectively permeable and poorly facilitate the uptake of macromolecules, leading to extremely low bioavailability [4]. Together, enzymatic instability and low epithelial permeability make oral delivery of biologics an intricate and largely unsolved pharmaceutical challenge.

Hydrogels, defined as three-dimensional hydrophilic polymer networks capable of absorbing large amounts of water, offer multifaceted benefits in overcoming oral delivery barriers. Their highly tunable chemical and physical properties allow for the encapsulation and protection of sensitive biologics against enzymatic degradation [1,6].

Additionally, hydrogels can be engineered to respond to specific GI stimuli, such as pH changes or enzymatic activity, enabling site-specific drug release at optimal absorption sites [5]. Smart hydrogel systems can also enhance mucoadhesion, prolonging residence time at the intestinal surface and improving drug permeation [7].

Thus, hydrogels are emerging as a promising platform for oral biologic delivery, bridging critical gaps between current therapeutic needs and biological barriers.

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Physiological and biological barriers to oral delivery of biologics

The oral administration of biologic drugs faces several formidable barriers within the gastrointestinal (GI) tract. Unlike small molecules, biologics have high molecular weights, complex tertiary structures, and are highly sensitive to environmental conditions, making their successful oral delivery extraordinarily challenging

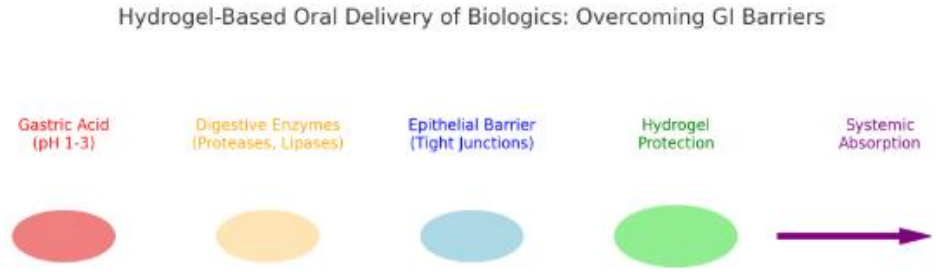

Figure 1: A visual diagram showing how hydrogel-based delivery overcomes gastrointestinal barriers like gastric acid, digestive enzymes, and epithelial barriers, leading to systemic absorption of biologics.

Enzymatic Degradation in the Gastrointestinal Tract

The GI tract is rich in proteolytic enzymes such as pepsin in the stomach and trypsin, chymotrypsin, and carboxypeptidases in the small intestine. These enzymes rapidly degrade protein-based biologics into inactive fragments before they can be absorbed [8].

Additionally, nucleic acid-based therapeutics, such as mRNA and siRNA, are highly susceptible to degradation by ubiquitous nucleases present throughout the GI system [9]. The enzymatic environment results in the rapid loss of structural integrity and biological activity of orally administered biologics.

Harsh Gastric pH

The stomach maintains a highly acidic environment (pH 1.5–3.5), designed to activate digestive enzymes and kill pathogens. However, this low pH also leads to denaturation and aggregation of protein drugs [10].

Biologics lacking robust tertiary stabilization rapidly unfold or become inactivated upon gastric exposure. Acidic conditions disrupt protein conformation and impair drug efficacy even before reaching the absorption site.

Poor Mucosal Permeability

Even if biologics survive enzymatic and pH-based degradation, they face a selectively permeable epithelial barrier. The tight junctions between epithelial cells restrict paracellular transport to very small molecules (<500 Da) [8].

As biologics typically exceed 1,000 Da (often 10,000+ Da for antibodies), their paracellular diffusion is negligible. Furthermore, endocytic transcytosis is inefficient for large macromolecules, leading to minimal systemic absorption. Low epithelial permeability drastically reduces oral bioavailability, often to less than 1% for unmodified biologics [9].

First-Pass Metabolism

After absorption, drugs pass through the hepatic portal vein to the liver where they may undergo first-pass metabolism. While small molecule drugs are typically metabolized enzymatically in the liver, biologics, if any fraction is absorbed, may still be cleared by hepatic or reticuloendothelial systems, further reducing their effective systemic concentrations [11].

Hydrogels as protective and responsive carriers

Hydrogels, by virtue of their unique structural and functional properties, present an advanced solution to the challenges faced in the oral delivery of biologics. Their highly hydrated, crosslinked polymer networks enable them to protect delicate molecules, facilitate controlled release, and adapt responsively to the dynamic gastrointestinal environment.

Hydrogels are three-dimensional hydrophilic polymeric networks capable of holding substantial amounts of water while maintaining structural integrity.
They can be broadly classified based on:

- Source: Natural (e.g., alginate, chitosan, gelatin) vs. synthetic (e.g., polyethylene glycol, polyvinyl alcohol)
- Crosslinking method: Physical (ionic, hydrogen bonding, hydrophobic) or chemical (covalent bonding)

Natural hydrogels offer superior biocompatibility, while synthetic hydrogels allow better control over mechanical strength and degradation rates [12,13].

Biocompatibility and Biodegradability

For oral delivery applications, hydrogels must be:

- Biocompatible, to avoid triggering immune responses.
- Biodegradable, ensuring they safely decompose into non-toxic byproducts after drug release.

Materials like alginate, hyaluronic acid, and gelatin have been widely employed due to their inherent biodegradability and minimal toxicity [14,15].

Protection Against Harsh GI Conditions

Hydrogels can **encapsulate biologics**, creating a physical barrier that shields them from:

- Acidic gastric pH
- Proteolytic enzymes
- Mechanical forces during digestion

Smart hydrogel designs incorporate pH-sensitive or enzyme-resistant matrices, ensuring the payload remains stable until reaching the small intestine or colon [16].

Example: pH-responsive hydrogels made from polymers like Eudragit® S100 resist stomach acid but dissolve at the higher pH of the intestine, releasing their drug payload precisely where absorption is optimized [17].

Stimuli-Responsive and Targeted Release

Next-generation hydrogels are engineered to be stimuli-responsive, enabling:

- pH-triggered swelling or disintegration
- Enzyme-triggered degradation for local release
- Temperature-sensitive release profiles

Such dynamic behavior ensures spatially and temporally controlled drug release, minimizing premature loss and maximizing therapeutic outcomes.

Example: Enzyme-sensitive hydrogels designed for inflammatory bowel disease (IBD) selectively degrade in the presence of matrix metalloproteinases overexpressed at inflamed sites.

Mucoadhesion and Prolonged GI Residence

Certain hydrogels are tailored to **exhibit mucoadhesive properties, allowing** them to stick to the intestinal mucosa. This prolongs residence time at absorption sites and enhances drug bioavailability by facilitating closer contact between the biologic and the absorptive epithelium.

Examples include hydrogels made from chitosan derivatives, which electrostatically interact with negatively charged mucosal surfaces, anchoring the carrier at the site of action.

Hydrogel formulations for biologics: state-of-the-art

The field of hydrogel-based oral delivery systems has seen remarkable innovation in recent years, particularly for fragile biologics such as insulin, mRNA vaccines, antibodies, and oral peptide vaccines. These

developments aim to enhance stability, improve mucosal absorption, and achieve controlled release to maximize therapeutic efficacy.

Protein and Peptide Delivery: Insulin as a Model Biologic

Insulin, a prototype biologic for non-invasive delivery research, has been extensively formulated within hydrogel systems to overcome enzymatic degradation and epithelial barriers.
Smart hydrogels, such as pH-sensitive poly(methacrylic acid)-based systems, protect insulin from gastric degradation and release it selectively in the intestine [18].
Newer studies have shown that nanocomposite hydrogels embedding insulin-loaded nanoparticles within a hydrogel matrix can further enhance bioavailability, achieving significant glucose-lowering effects in animal models [19].

Oral Vaccines Using Hydrogel Systems

The COVID-19 pandemic accelerated innovation in oral vaccine delivery platforms. Hydrogels are now being explored for oral mRNA and subunit vaccines, providing:

- Protection against GI degradation
- Controlled release to Peyer's patches or lymphoid tissue
- Enhanced mucosal immunity

For example, hydrogel microspheres loaded with mRNA vaccines demonstrated the ability to elicit robust IgG and mucosal IgA responses when administered orally [20].

Gene Therapy: Oral Delivery of mRNA and siRNA

Delivering mRNA and small interfering RNA (siRNA) orally requires exceptional protection and cellular targeting.
Hydrogel carriers engineered with cationic polymers and enzyme-responsive linkers enable:

- Stable encapsulation of nucleic acids
- Protection from ribonucleases
- pH-triggered release into intestinal cells [21].

Research efforts have successfully used chitosan-alginate hydrogels for oral mRNA vaccination against viral infections, paving the way for non-invasive gene therapies.

4. Monoclonal Antibodies and Nanobodies

While oral delivery of antibodies faces significant challenges due to their size and sensitivity, hydrogel encapsulation shows promise:

- Protects antibodies from proteolysis
- Sustains local delivery in the gut for treating diseases like inflammatory bowel disease (IBD)

New formulations using thiolated hydrogels have enhanced mucosal penetration and preserved antibody activity after transit through the GI tract [22].

Design strategies for hydrogel-based oral systems

The rational design of hydrogel-based oral drug delivery systems is crucial to overcoming biological barriers and enhancing the bioavailability of biologics. Strategies focus on protecting the payload, prolonging mucosal residence, and triggering controlled release under specific gastrointestinal conditions.

Mucoadhesive Hydrogels

Mucoadhesive hydrogels can stick to the mucosal surfaces of the gastrointestinal tract, thereby:

- Prolonging retention time at the absorption site
- Reducing drug clearance
- Facilitating direct drug transport across the epithelial barrier

Chitosan-based hydrogels and thiolated polymers are popular materials for mucoadhesion due to their ability to interact with negatively charged mucins [23]. Mucoadhesion also enhances paracellular transport by opening tight junctions temporarily, improving the uptake of macromolecules like insulin and siRNA.

pH-Sensitive Hydrogels

pH-sensitive hydrogels are designed to protect drugs in the stomach (pH ~1.5-3.5) and release them in the intestine (pH ~6.5-7.5).
Typical polymers include:

- Poly(methacrylic acid) derivatives
- Eudragit® polymers
- Polyacrylic acid blends

These hydrogels remain collapsed in acidic environments and swell or dissolve under neutral to

basic conditions, enabling site-specific release of biologics such as vaccines and proteins.

3. Enzyme-Responsive Hydrogels

Hydrogels responsive to intestinal or bacterial enzymes provide localized release:

- Matrix metalloproteinase (MMP)-sensitive hydrogels for inflamed tissues
- Amylase- and protease-sensitive hydrogels in the gut

This strategy ensures that therapeutic payloads are selectively released where disease-specific or microbiota-derived enzymes are overexpressed [24].

Example: An oral hydrogel vaccine was engineered to degrade upon contact with intestinal proteases, enhancing delivery to Peyer's patches.

Nanohydrogels / Nanoparticle-Embedded Hydrogels

Embedding nanoparticles inside hydrogel matrices combines the advantages of both systems:

- Hydrogels protect nanoparticles from gastric destruction
- Nanoparticles provide enhanced cellular uptake and endosomal escape once released

Thermo-responsive hydrogels loaded with lipid nanoparticles carrying insulin, or polymeric nanoparticles carrying mRNA, have demonstrated remarkable improvements in oral bioavailability [25,26].

This multi-layered protection and release system represents a highly promising future strategy for oral biologic delivery.

Pharmacokinetics and in vivo performance of hydrogel-delivered biologics

Understanding the in vivo behavior of hydrogel-based drug delivery systems is essential to optimize therapeutic outcomes. Critical parameters include drug absorption, bioavailability, residence time, and systemic distribution. Several animal studies and early human trials have demonstrated the potential of hydrogels to significantly improve oral biologic delivery.

Enhanced Stability and Bioavailability

One of the core advantages of hydrogel carriers is their ability to protect biologics from gastrointestinal degradation, thereby maintaining drug integrity during transit.

For example, insulin-loaded hydrogels demonstrated significantly higher plasma insulin levels and prolonged glucose-lowering effects compared to unprotected insulin in diabetic rat models [27].

Similarly, oral mRNA vaccines formulated with pH-sensitive hydrogels exhibited up to a 10-fold increase in bioavailability compared to naked mRNA administration [28].

Pharmacokinetic Profiles: Sustained and Controlled Release

Hydrogels can modulate the **rate of drug release**, leading to:

- Delayed Tmax (time to reach peak plasma concentration)
- Lower Cmax (peak plasma concentration)
- Prolonged drug half-life (t½)

In vivo studies with thermo-responsive nanohydrogel systems for oral protein delivery showed sustained release profiles with therapeutic plasma levels maintained for over 24 hours [29].

Absorption Enhancement Mechanisms

Hydrogels enhance the paracellular transport of macromolecules by:

- Temporarily opening tight junctions (especially with chitosan-based systems)
- Adhering to mucosal surfaces for localized absorption (mucoadhesive hydrogels)

Experimental results showed that thiolated hydrogels could increase insulin permeability across Caco-2 cell monolayers by nearly 5-fold (Yu et al., 2023).

Animal Models and Translational Studies

Various animal models have been employed to validate hydrogel formulations:

- Rats and mice for initial pharmacokinetic evaluations
- Pigs and dogs for closer approximation of human GI physiology

- Non-human primates for preclinical validation of vaccine and antibody delivery

For example, oral delivery of monoclonal antibodies via complexation hydrogels in mice preserved therapeutic bioactivity and successfully suppressed inflammatory bowel disease markers [30-32].

Toward Human Trials

Although most studies are at the preclinical stage, early-phase clinical evaluations are emerging.
Anselmo and Mitragotri (2019) reported that phase I trials of hydrogel-encapsulated oral biologics have shown acceptable safety profiles and promising bioavailability improvements over conventional formulations [8].

Emerging trends and future directions

Recent advances in hydrogel-based oral delivery systems for biologics have opened new frontiers in non-invasive therapeutic strategies. The field is witnessing a shift toward smart, multi-responsive hydrogels that can sense and react to multiple gastrointestinal stimuli such as pH, enzymes, redox environment, and even microbial signals. Microbiome-responsive hydrogels, designed to release drugs in response to specific bacterial metabolites, represent a promising avenue for personalized treatments, particularly in inflammatory and metabolic diseases. Additionally, the integration of artificial intelligence and machine learning tools is enabling the predictive design of hydrogel systems, optimizing drug release kinetics, stability, and targeting based on vast biological and materials databases. Multi-compartment systems like hydrogel-in-hydrogel structures and nanoparticle-loaded hydrogels are being developed to allow simultaneous or sequential delivery of multiple biologics, such as a combination of mRNA vaccines and immunotherapies. Regulatory agencies are gradually adapting to these innovations by creating new frameworks for assessing complex, bioresponsive materials. Meanwhile, early clinical trials are starting to explore the real-world potential of these platforms in delivering insulin, monoclonal antibodies, and oral vaccines. Nevertheless, challenges such as manufacturing scalability, batch-to-batch reproducibility, long-term stability, and ensuring immunological safety remain substantial. Overall, hydrogel-based oral delivery systems represent a rapidly maturing platform that could revolutionize biologic therapy, bringing closer the vision of non-invasive, targeted, and patient-centric treatment regimens.

Conclusion

Hydrogel-based oral delivery systems for biologics represent a transformative advance in pharmaceutical science, offering a viable solution to the long-standing challenges of enzymatic degradation, low epithelial permeability, and systemic instability. Through intelligent design strategies encompassing mucoadhesion, pH responsiveness, enzyme sensitivity, and nanoparticle embedding, hydrogels have demonstrated remarkable success in preclinical models by protecting biologics and enhancing their bioavailability. Regulatory bodies are increasingly recognizing the potential of such systems, though standardization of manufacturing processes, long-term stability assurance, and rigorous clinical validation remain essential steps for widespread adoption. Emerging trends, such as microbiome-responsive hydrogels, AI-driven formulation optimization, and personalized therapeutic designs, promise to further elevate the field, bringing non-invasive, patient-friendly biologic therapies into mainstream clinical practice. As research continues to overcome the remaining technical and translational hurdles, hydrogel-based oral delivery platforms are poised to redefine the future of drug delivery, ultimately improving patient compliance, therapeutic outcomes, and the global accessibility of advanced biologics.

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Conflict of Interest

None declared.

Author Contributions

All the authors contributed to the study.

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