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Addressing the challenges and advancements in oral drug delivery systems for biopharmaceuticals: A comprehensive review of recent developments and future directions

Ibrahim Abdullah Hamzy
KSA, National Guard Health Affairs

Abdulelah Ibrahim Alqhoson
KSA, National Guard Health Affairs

Anas Mohammed Aljarbou
KSA, National Guard Health Affairs

Mohammed Abdulrahman Alhajri
KSA, National Guard Health Affairs

***Abstract*---Background:** Drug delivery systems have evolved to improve the administration, efficacy, and safety of pharmaceuticals. Traditional methods such as intravenous (IV), intramuscular (IM), and oral delivery each face unique challenges and benefits. Among these, oral drug delivery remains a significant focus due to its convenience, patient compliance, and potential for sustained release. However, biopharmaceuticals, particularly vaccines and large molecules, present specific challenges to oral administration. **Aim:** This review aims to comprehensively evaluate the current advancements in oral drug delivery systems for biopharmaceuticals, highlighting recent innovations and their potential to address existing challenges. It seeks to explore the effectiveness of various oral delivery strategies and their implications for improving drug bioavailability and therapeutic outcomes. **Methods:** The review consolidates recent developments in oral drug delivery, including innovations in delivery devices such as intestinal patches, microneedle capsules, and particulate systems. It examines the biological barriers encountered by oral drugs, such as the gastrointestinal (GI) tract's acidic environment and enzymatic degradation, and discusses technological advancements designed to overcome these obstacles. **Results:** Key advancements include the development of pH-responsive hydrogels, microneedle-based delivery systems, and novel particulate carriers. These innovations aim to

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protect drugs from harsh GI conditions, enhance drug absorption, and provide controlled release. Despite these advancements, challenges such as drug stability, mucus turnover, and the efficient targeting of large molecules remain significant. **Conclusion:** Oral drug delivery systems have seen substantial progress, particularly in biopharmaceutical applications. Innovations such as advanced microencapsulation techniques and novel delivery devices offer promising solutions to the challenges of oral administration. However, further research is needed to address remaining technical and biological barriers, improve drug stability, and ensure effective delivery of large molecules and vaccines.

***Keywords*---**Oral drug delivery, biopharmaceuticals, pH-responsive hydrogels, microneedles, particulate carriers, drug stability, gastrointestinal barriers.

Introduction

Intravenous (IV), intramuscular (IM), intranasal (IN), intradermal (ID)/transdermal, and oral administration are the main drug delivery techniques. Furthermore, particular delivery methods like ocular delivery have been created to allow for targeted, localized medication administration, reducing systemic side effects [1]. Every delivery technique faces different challenges that impact the administration of drugs. Moreover, the incorporation of pharmaceuticals into delivery systems has the potential to greatly improve drug retention, precise targeting, and effectiveness of treatment. With an emphasis on oral delivery methods because of their potential benefits, this paper offers a thorough overview of different administration routes. We go over the main problems with these techniques and look at new developments meant to solve them.

The drug's properties and the process of drug absorption play a critical role in choosing the best delivery methods to maximize bioavailability and efficacy. For immunizations, for instance, IM and ID routes are frequently utilized, depending on the intended immunological response. On the other hand, because oral and IN vaccination methods can elicit both mucosal and systemic immune responses, there is a great deal of interest in these approaches from researchers in the academic and industrial sectors. Bypassing physiological obstacles to absorption, intravenous (IV) injection permits the medicine to enter the bloodstream immediately through needles, offering the best bioavailability and fastest onset of action among all delivery methods. Therefore, non-invasive techniques are typically used for long-term therapy and chronic administration, whereas intravenous (IV) administration is preferable for acute and emergency conditions [2]. Through the first line of defense—the skin—drug absorption from intramuscular injections is facilitated by the muscles' thick blood vascular network [3]. But while intramuscular (IM) injections circumvent the gastrointestinal (GI) system in contrast to oral delivery, they can also cause pain, needle fear, hazardous needle practices, the necessity for specialized staff, muscle atrophy, and damage to bones and nerves [4]. Furthermore, close monitoring is

required to minimize side effects when administering IM directly into the bloodstream [5,6].

Delivery issues are unique to biopharmaceuticals, especially vaccinations. Due to the damaging effects of proteases in the GI tract and the restricted permeability of big macromolecules across mucosal barriers, the majority of vaccinations are delivered intraperitoneally (IM) via injection [7, 8]. Drugs have been successfully preserved in a variety of biological settings by using silica and polymer mesoporous structures, which also regulate the release behavior of topical injections [9,10,11]. However, due to reduced immunogenicity and bioavailability, intramuscular (IM) injection is less appropriate for peptides and proteins than subcutaneous or IV methods [12]. Despite being widely used in medicine and having the ability to trigger an immune response through a local depot, IM vaccination is not as suitable for peptides and proteins because of the possibility of drug aggregation [13].

Drugs are delivered into the bloodstream via the transdermal route by passing through the layers of skin [14]. Three pathways are involved in absorption: intercellular, transcellular, and transappendageal. The latter two allow permeation through the stratum corneum, whereas the former involves sweat ducts or hair follicles [15]. This approach offers sustained plasma drug levels, circumvents GI metabolism and associated complications, and facilitates quick withdrawal in the event of adverse reactions. Utilizing nanoparticles (NPs) in nano/micro-engineered needle patches is one recent development that aims to lower the bacterial dangers related to transdermal delivery [16]. In order to overcome structural and optical inconsistencies, novel deposition-etching techniques for flexible silicon nanoneedles have been devised, and nanoimprint lithography has been offered as a solution to meet commercial requirements for these devices [17]. Large molecules (>500 Da) have trouble passing through the stratum corneum, hence the principal obstacle to successful medication delivery still stands in the way of these advancements. To promote drug absorption, both chemical and physical enhancers have been devised; nonetheless, toxicity and skin irritation are still issues. Though the processes underlying these effects and interactions are still unknown, systematic investigations have discovered key rules for creating new formulations [18,19,20, 21].

By injecting medication straight into the veins, intravenous administration avoids biological, chemical, or physical obstacles and allows for rapid absorption. This approach is perfect for emergency scenarios since it provides exact control over dosage and administration speed [22]. However, there are dangers associated with IV administration, including thrombosis, phlebitis, circulatory overload, infection, and needle-related harm [23, 24]. Since it has about 100% bioavailability, it is frequently utilized for biopharmaceuticals; nevertheless, because of difficulties in eliciting effective immune responses and restrictions on mass administration, it is less appropriate for vaccines [25].

Giving medications to the highly vascularized nasal mucosa in order to facilitate systemic absorption is known as intranasal drug delivery [26]. This pathway is especially significant for neurological therapies since it gets over the blood-brain barrier (BBB). IN administration encounters physiological and physicochemical

obstacles, including as nasal mucus and clearance, pH, drug-mucus interactions, and mucus viscosity, even if it is beneficial for local disorders and has fewer systemic effects. By removing these obstacles, mucoadhesive microencapsulation devices have been created to improve medication bioavailability [27]. Mucociliary clearance, however, shortens the duration of drug residence, and big molecule administration is still difficult. Although improvements in skin permeability for transdermal distribution have been made through chemical and physical means, worries about safety and irritation still exist. Although the physical and physiological features of the nasal passage limit efficiency and clinical use, aerosol sprays are frequently chosen for IN delivery. Low bioavailability is a major concern [28,29,30,31].

Oral Route

Among the diverse drug delivery pathways, the oral route has garnered significant attention due to its distinct advantages, including controlled and sustained delivery, ease of administration, suitability for solid dosage forms, high patient adherence, and enhanced immune responses in the case of vaccines [32,33,34,35,36]. Additionally, the oral cavity possesses a substantial surface area (>300 m^2) covered by a viscous mucosal layer, facilitating drug adhesion and subsequent absorption [37,38]. Drugs embedded within this mucus are shielded from the shear forces exerted by gastric fluids [39]. The human intestinal epithelium is highly absorptive due to the abundance of enterocytes, particularly microfold cells (M cells) situated over Peyer's patches, which are lymphoid structures within the small intestine [40,41,42,43,44]. However, compared to other administration routes, oral drug absorption is more intricate. For effective absorption, drugs must be soluble in gastric fluid to be absorbed either in the stomach, the small intestine, or the colon. Oral drugs can be absorbed through four primary mechanisms: transcellular, paracellular, carrier-mediated transcellular, and facilitated transport, with the transcellular route being predominant. The challenges associated with oral drug absorption extend beyond the intestinal barriers to include hepatic barriers once drugs enter the vessels beneath the intestinal epithelium. Consequently, oral drugs are generally unsuitable for emergency situations due to their slower absorption rates and the complex barriers they encounter.

Despite the oral route being highly desirable for small therapeutic molecules, there are relatively few oral vaccines available due to the harsh conditions within the gastrointestinal (GI) tract, which can lead to the degradation or denaturation of active antigens. Nonetheless, the potential for mucosal immunity induced by oral and nasal routes has spurred interest in oral vaccines [49]. Furthermore, the convenience and other advantages of oral delivery make it a promising approach for mass vaccination programs. The key inductive sites in the GI tract include Peyer's patches, lymphoid follicles in lymph nodes, and antigen-presenting cells (APCs). The mucosal immunity in the intestines resembles that of the nasal mucosa. However, the main obstacles for vaccine delivery are the variable pH along the GI tract and the presence of various enzymes, which complicate the penetration through mucus and reach the gut-associated lymphoid tissue (GALT) [50]. Additionally, the mucosa may alter the structure of proteins and peptides through various interactions [38]. Consequently, there is a need for advanced

delivery vehicles and formulations to enhance immunogenicity and achieve the required therapeutic efficacy. Currently, seven live oral vaccines have been approved by the FDA.

To address the growing demand for biopharmaceutical oral products, research has focused on developing novel oral delivery devices. Although still in the early stages, recent innovations include intestinal patch systems, microneedle capsules, and particulate systems [51]. Intestinal patch systems function as unidirectional drug release depots, akin to microdevices adhered to the intestinal wall [52]. Microneedle capsules enhance drug penetration by directly piercing the mucosa with microneedles, and recent advancements include methods for microneedle inflation in response to pH changes [53]. Particulate systems, the most common oral delivery vehicles, have been explored for encapsulating and targeting a wide range of therapeutics. These technologies remain predominantly at the preclinical stage, necessitating further research to address existing technical challenges and establish clinical feasibility.

Challenges Associated with Oral Delivery

Oral drugs are absorbed through the gastrointestinal (GI) tract, which functions as a conduit. While some drugs exert local effects within the gut, the majority are absorbed into the bloodstream and distributed systemically. The GI tract is divided into the upper and lower sections. The upper GI tract comprises the oral cavity, pharynx, esophagus, stomach, and the initial segment of the small intestine (duodenum), while the lower GI tract includes the remainder of the small intestine (jejunum and ileum) and the large intestine (cecum, colon, and rectum) [54,55]. The GI tract's structure is consistent across these segments, with the lumen surrounded by smooth muscle cells, mucus, submucosa, and several muscle layers [56]. The mucosal layer, which lines the inner GI tract, consists of epithelial cells, lamina propria, and muscularis mucosae, playing critical roles in the transport of food and drug molecules as well as gastrointestinal immunity [54,55]. The extensive absorption area and prolonged residence time in the small intestine, particularly in the jejunum and ileum, enhance drug absorption compared to the duodenum [57,58].

Several environmental factors influence drug integrity and absorption, including segment length, pH, mucus thickness, drug residence time, and bacterial diversity in different segments [38,59,60]. The obstacles to oral drug administration can be broadly categorized into biological barriers and technical challenges. Biological barriers encompass any biological factors that cause denaturation or impede the absorption of orally administered drugs. Technical challenges involve difficulties in the fabrication of oral delivery devices, either related to creating specific properties to address biological barriers or issues with scaling up and commercialization. These aspects will be elaborated upon in the following sections.

Biological Barriers

Orally administered substances encounter three primary biological environments within the gastrointestinal (GI) tract: the lumen, mucus, and tissue. Each environment interacts with the drug molecules.

Lumen

The initial biological barrier for orally administered drugs is the acidic environment of the stomach (pH 1–2.5), which can denature or depurinate most drug molecules, significantly reducing their effectiveness [61,62,63,64]. In addition to stomach acid, gastric enzymes such as pepsin and gelatinase can degrade biopharmaceuticals. pH-responsive hydrogels can encapsulate drugs to protect them from the harsh acidic conditions and gastric enzymes. These hydrogels can remain intact in unfavorable conditions and release the drug in response to environmental stimuli like pH changes. For example, Yamagata et al. demonstrated that pH-sensitive hydrogel microparticles (MPs) can effectively preserve sensitive drugs like insulin from gastric and intestinal enzyme fluids [65]. Similarly, Cerchiara et al. developed an oral pH-responsive microencapsulation system that protects drugs from both acidic and enzymatic environments [66].

Pancreatic enzymes, synthesized in the pancreas and secreted into the intestinal lumen, include lipase, trypsin, amylase, and peptidases. These enzymes, particularly prevalent at the duodenum's entrance, can decompose nucleic acids and diminish the stability of biomolecules in the stomach [67,68]. However, they are not considered a major challenge for oral delivery due to their primarily duodenal presence and decreasing concentration in the jejunum and beyond [69]. Additionally, the short transit time through the duodenum limits enzyme exposure, and the lower pH in the duodenum compared to the lower small intestine helps avoid unintended drug release [71]. For example, Lozoya-Agullo et al. used poly(lactic-co-glycolic) acid (PLGA) nanoparticles for colon delivery and successfully avoided premature release in the duodenum due to insufficient pH [72].

Apart from acidic and enzymatic degradation, the lumen can also damage drug molecules through osmotic stresses, peristalsis, and shear stresses from gastric juice flow, which can lead to mechanical degradation [32,38]. Flowing gastric juice can reduce drug contact time with the epithelial layer, impeding absorption [67]. Biological agents such as viruses, vaccines, and cells are particularly susceptible to mechanical damage. Valon et al. reported that shear stresses and compaction can induce apoptosis and cell death [73], while Choi et al. found that hyperosmotic pressure can compromise virus integrity in acidic conditions [32]. Microencapsulation can mitigate these issues, with recent studies showing that incorporating nanoparticles, such as cellulose nanocrystals (CNCs), into hydrogels significantly enhances mechanical strength and stability [74,75]. Despite improvements, the distribution and impact of reinforcing agents within hydrogels remain inadequately understood.

Technical Challenges

Technical challenges in oral drug delivery systems involve various aspects, including the design and development of devices, achieving sustained delivery, and scaling up systems for commercial production. Here, we'll explore these challenges in detail:

Design and Development of Oral Delivery Devices

Device Design Considerations:

- **Size and Shape:** Oral delivery devices must be designed to be compatible with the gastrointestinal (GI) tract. Devices need to be small enough to pass through the GI tract without causing discomfort or obstruction. The shape can influence the release rate and site of absorption [113,114].
- **Material Selection:** Materials used in oral delivery devices must be biocompatible and capable of withstanding the harsh conditions of the GI tract. They should also provide a controlled release of the drug. Common materials include polymers like poly(lactic-co-glycolic acid) (PLGA) and hydrogels [115,116].
- **Release Mechanism:** Designing devices that provide a controlled release of drugs over time is crucial. This may involve mechanisms such as diffusion, erosion, or osmotic pressure. For example, osmotic pump systems release drugs at a controlled rate by exploiting osmotic pressure [117,118].

Integration with Existing Technologies:

- **Compatibility with Food Intake:** Devices must be designed to integrate well with the presence of food in the GI tract. This involves ensuring that the device can function effectively in the presence of gastric acids and enzymes that are influenced by food intake [119,120].
- **Interaction with Existing Drugs:** For combination therapies, devices must be able to co-deliver multiple drugs without interactions that could affect efficacy or safety [121].

Sustained Delivery Strategies

Challenges in Sustained Delivery:

- **Maintaining Stability:** Drugs must remain stable over extended periods. This involves protecting drugs from degradation due to environmental factors such as pH changes and enzymatic activity [122,123].
- **Controlled Release:** Achieving a controlled release profile that matches the therapeutic needs of the drug can be challenging. This requires precise engineering to ensure that drugs are released at the right rate and location in the GI tract [124,125].

Technologies for Sustained Delivery:

- **Hydrogels and Nanoparticles:** These systems can provide sustained drug release by swelling in the presence of water or by slowly degrading over time. Hydrogels can be designed to respond to environmental stimuli such as pH changes [126,127].

- **Microencapsulation:** Encapsulating drugs in microspheres or nanoparticles can protect them from degradation and allow for controlled release. Techniques such as solvent evaporation and coacervation are commonly used [128,129].

Solvent-Free Microencapsulation Techniques

Need for Solvent-Free Methods:

- **Environmental and Health Concerns:** Solvent-free methods are becoming increasingly important due to environmental and health concerns associated with traditional solvent-based techniques. These methods aim to minimize the use of harmful solvents, reducing potential toxicity and environmental impact [130,131].
- **Efficiency and Stability:** Solvent-free techniques can offer advantages in terms of efficiency and stability of the final product. They can also improve the safety profile of the drug delivery systems by avoiding the residual solvents that may affect drug efficacy and safety [132,133].

Examples and Applications:

- **Electrospinning and Melt Extrusion:** Methods such as electrospinning and melt extrusion are used to create drug-loaded fibers or particles without the use of solvents. These techniques can be applied to produce sustained release formulations with controlled release properties [134,135].
- **Supercritical Fluid Technology:** This technique uses supercritical fluids as an alternative to traditional solvents, allowing for the production of microencapsulated drugs with improved properties and reduced environmental impact [136,137]. By addressing these technical challenges, researchers and developers can advance the field of oral drug delivery and improve therapeutic outcomes.

Oral Delivery Devices and Materials

The devices developed for oral drug administration can be classified into several categories: intestinal patches, gastrointestinal microneedles, and particulate carriers (including micro/nanoparticles, micelles, and liposomes).

Intestinal Patches

Intestinal patches are millimeter-sized mucoadhesive blankets that attach to the inner walls of the GI tract, providing a drug reservoir at the target. These patches can protect the drug from the harsh environment and luminal loss, improving drug bioavailability by creating a unidirectional diffusion regime towards the intestinal tissue [121]. Insulin, interferon-α, and calcitonin are examples of drugs investigated for delivery using such devices [121]. Key factors to consider for intestinal patches include mucosal adhesion properties, loading capacity, release rate, and release direction. Mitragotri et al. utilized mucoadhesive polymers, such as Eudragit copolymers or pectin, to prolong the gastric residence time of these devices [122]. They also employed impermeable ethyl cellulose sheets to create a unidirectional release pattern and seal the opposite side of the patches. Shen et al. demonstrated that incorporating drug-loaded microspheres into patches,

rather than direct drug loading, can significantly enhance control over drug release behavior [123]. Toorisaka et al. developed a lipophilic drug-in-oil formulation to improve the system's compatibility with intestinal cell lines and enhance insulin absorption [124]. They later addressed retention time issues by designing a bilayer patch with a drug-impermeable layer for unidirectional release and a mucoadhesive layer to prolong gastric residence [125]. Despite over two decades of development, these oral patches have not received as much research attention as other designs, such as particulate carriers. They are mainly applicable in the duodenum, where solid boluses of digested food can detach the patch from the lumen wall in later parts of the GI tract, significantly decreasing transient time. The mucus turnover cycle also limits their application for sustained delivery.

Gastrointestinal Microneedles

Intestinal microneedles are a recent development in oral delivery devices. Originally designed for transdermal delivery, microneedles have been extended to other administration routes, including the vagina, anus, and scalp [126]. In 2014, Ma et al. employed microneedles for oral vaccine delivery to the mouth cavity, marking the first use of microneedles for oral administration [127]. They tested the system with HIV antigens (DNA vaccines and virus-like particles) and compared the immune response to intramuscular injection, finding that only orally administered agents induced a significant antigen-specific IgA response in saliva. A limitation of this design is its applicability only to the oral cavity rather than the entire GI tract. In 2015, Traverso et al. developed orally ingested microneedles to overcome GI tract barriers and improve drug bioavailability [128]. They claimed that their device could be safely excreted from the GI tract, showing significant improvements in insulin bioavailability compared to subcutaneous administration. However, this system requires further study, particularly through clinical trials, as it is still a relatively new approach.

Particulate Carriers

Spherical carrier designs, including micelles, liposomes, and microparticles (MPs), are among the most commonly studied oral delivery vehicles. Micelles are colloidal carriers (5–100 nm) designed to improve the aqueous solubility of hydrophobic pharmaceuticals and facilitate their oral delivery. Made of amphiphilic molecules, micelles encapsulate hydrophobic ingredients inside their core, with hydrophilic segments oriented on the outer surface. Dabholkar et al. developed a polyethylene glycol-phosphatidylethanolamine conjugate that increased the water solubility of paclitaxel (an anticancer drug) up to 5000 times [129]. Due to their small size (20–80 nm), micelles can penetrate various tissues spontaneously, improving permeation efficiency and retention time. Yu et al. developed dual-responsive (pH and light) micelles to enhance passive tumor targeting of doxorubicin and address drug resistance [130]. These micelles improved drug penetration into tumors and prolonged blood circulation. Suzuki et al. used cationic micelles for doxorubicin encapsulation, achieving up to a 40-fold increase in in vitro drug penetration [131]. Despite their potential, micelles have seen limited commercialization, with clinical trials primarily focused on cancer therapies due to safety concerns and the physicochemical interactions with mucus [132]. Liposomes are phospholipid

vesicles (>200 nm) capable of encapsulating both hydrophobic drugs in their hydrophobic compartment and hydrophilic drugs in their inner core. They can be chemically modified with antibodies for improved target specificity, although they may suffer from a short life cycle in blood circulation due to accumulation in the liver [133].

Microparticles (MPs) are another common oral delivery architecture. Materials used in oral microencapsulation systems can be classified into polymers and ceramics. Ceramics, such as silica, alumina, and calcium phosphate, are bio-inert and safe for delivery applications. For example, calcium phosphate carriers have been used for delivering cisplatin, methotrexate, and hydrocortisone acetate, while silica nanoparticles are utilized in chemotherapy [134]. Polymers, especially hydrogels, are attractive due to their controllable composition, tunable mechanical properties, water absorption, and stimuli-responsivity [135,136,137,138,139]. Porosity is a critical feature in hydrogels, affecting mechanical properties, material flow, and swelling ratio. Torres-Lugo et al. controlled the release rate of salmon calcitonin from poly-(methacrylic acid) (PMAA) MPs by adjusting the swelling ratio and mesh size [140]. Methods to increase hydrogel porosity include leaching template materials, decreasing crosslinking sites, and lyophilizing absorbed liquids to create pores [141,142,143,144,145,146,147]. Pore size and geometry influence nutrient transfer rates and cell migration patterns, making precise control over porosity and pore morphology crucial [149,150,151,152,153,154]. France et al. recently reviewed methods for creating macroporous hydrogels [143].

Sustained Delivery

Mucoadhesive Carriers

Maintaining a constant drug concentration in the bloodstream is crucial for effective treatment, as fluctuations can lead to toxicity or ineffective treatment. Sustained delivery methods help address these issues by ensuring a more stable drug release profile. In oral delivery systems, mucoadhesive carriers are designed to adhere to the mucosal surfaces of the gastrointestinal (GI) tract, extending the release of the drug.

Materials and Mechanisms:

1. **Mucoadhesive Hydrogels**: These materials can be cationic, like chitosan-based hydrogels, or thiol-functionalized, which bond to mucin glycoprotein. Despite their ability to increase retention time compared to controls, they often only provide a modest increase in delivery duration due to the rapid turnover of mucus in the intestine.
2. **pH-Responsive Polymers**: Microencapsulated drugs often use pH-sensitive polymers that release their cargo only when exposed to pH values higher than the polymer's pKa (typically >6). While the pH in many parts of the intestine is above this threshold, this can still lead to incomplete drug release in some cases.

3. **Challenges with Mucoadhesive Systems**: The effectiveness of these systems can be limited by the friction they cause against the GI tract walls, which can impact the device's performance and patient comfort.

Recent Gastric-Resident Architectures
Recent innovations aim to enhance drug retention and sustained release by creating larger structures that remain in the GI tract for extended periods.

1. **Expandable Structures**: One approach involves devices that expand to a diameter larger than the pyloric sphincter (~1.5 cm), preventing passage into the small intestine. Early versions faced issues like lumen obstruction and the need for surgical removal due to non-degradable materials.
2. **Elastic Foldable O-Rings**: Zhang et al. developed an elastic O-ring made from various hydrogels. This ring, encapsulated in a degradable capsule, releases drugs over several days as it degrades in the stomach. Although the device showed promising results, concerns include potential blockage of the GI tract and the challenge of removing the device if adverse effects occur.

Solvent-Free Microencapsulation

Multiemulsion Systems
Microencapsulation using multiemulsion systems (e.g., W/O/W and O/W/O) aims to minimize drug contact with organic solvents, which can cause denaturation. Traditional multiemulsion techniques faced difficulties with control and stabilization, and issues like drug denaturation due to shear stresses and temperature changes.

Microfluidic Devices:
Microfluidic devices have improved this technology by allowing for highly uniform microparticles with minimal polydispersity and stability without the need for mechanical agitation or sonication. These devices facilitate controlled emulsion formation and have potential applications in cell encapsulation. However, challenges such as channel clogging and low throughput remain, hindering their commercial scale-up.

Pored and Hollow Microencapsulation Systems

Another approach to solvent-free microencapsulation involves creating hollow microparticles with separate drug loading processes:

1. **Template-Based Methods**: These involve coating solid templates with polymers, then removing the templates to leave hollow spheres. Issues with these methods include low drug loading efficiency due to poor diffusion through solid shells.
2. **Solvent Evaporation Method**: Hyuk Im et al. developed a method where polystyrene particles are swollen in organic solvents, then frozen and evaporated, creating hollow interiors and surface pores for drug loading. The pores can be closed through thermal treatment.
3. **Ultrasonic Emulsification**: Kumar et al. used ultrasonic emulsification to create single-pored microparticles. This method allows for drug loading under favorable conditions and seals the pores through freeze-drying,

reducing the risk of thermal denaturation. These advancements in microencapsulation technology offer promising avenues for improving drug delivery, particularly for sensitive biopharmaceuticals and large biomolecules.

Conclusion

The review of oral drug delivery systems reveals significant strides in addressing the challenges associated with biopharmaceutical administration. Oral delivery, with its non-invasive nature and patient convenience, remains a highly desirable method, particularly for chronic and long-term treatments. However, the complexity of gastrointestinal (GI) absorption poses substantial hurdles, including acidic environments, enzymatic degradation, and the need for effective mucosal penetration. Recent advancements have introduced innovative solutions to enhance oral drug delivery. pH-responsive hydrogels and nano/micro-engineered devices, such as intestinal patches and microneedle capsules, offer improved drug protection and targeted release. These technologies aim to circumvent the harsh conditions of the GI tract and enhance bioavailability. For instance, microneedles have demonstrated potential in delivering vaccines and large molecules by piercing the mucosal barriers and improving drug absorption. Despite these advancements, challenges persist. The efficiency of oral vaccines is still limited by the degradation of antigens in the GI tract and the variability in pH along the digestive system. Additionally, the development of devices that remain in the GI tract for extended periods without causing discomfort or adverse effects is crucial for sustained drug release. Technical issues, such as scaling up manufacturing processes and ensuring stability and safety, need further investigation. In summary, while oral drug delivery systems for biopharmaceuticals have made remarkable progress, continued research and innovation are essential. Addressing the remaining challenges will be key to optimizing these systems, improving patient outcomes, and expanding the scope of oral delivery applications.

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التعامل مع التحديات والتطورات في أنظمة توصيل الأدوية عن طريق الفم للمنتجات البيولوجية: مراجعة شاملة للتطورات الحديثة والاتجاهات المستقبلية

الملخص:

الخلفية :تطورت أنظمة توصيل الأدوية لتحسين طريقة الإدارة والفعالية والسلامة للأدوية. تواجه الطرق التقليدية مثل التوصيل الوريدي (IV) والتوصيل العضلي (IM) والتوصيل عن طريق الفم تحديات وفوائد فريدة. من بين هذه الطرق، يظل توصيل الأدوية عن طريق الفم محوراً مهماً بسبب راحته، والتزام المرضى، وإمكانية الإفراج المستمر. ومع ذلك، تقدم المنتجات البيولوجية، وخاصة اللقاحات والجزيئات الكبيرة، تحديات خاصة للإدارة عن طريق الفم.

الهدف :تهدف هذه المراجعة إلى تقييم التطورات الحالية في أنظمة توصيل الأدوية عن طريق الفم للمنتجات البيولوجية بشكل شامل، مع تسليط الضوء على الابتكارات الحديثة وإمكاناتها لمعالجة التحديات القائمة. وتسعى إلى استكشاف فعالية استراتيجيات التوصيل عن طريق الفم المختلفة وتأثيرها على تحسين توافر الدواء والعلاج.

الطرق :تجمع المراجعة بين التطورات الحديثة في توصيل الأدوية عن طريق الفم، بما في ذلك الابتكارات في أجهزة التوصيل مثل اللصقات المعوية، وكبسولات الإبر الدقيقة، والأنظمة الجزيئية. كما تفحص الحواجز البيولوجية التي تواجه الأدوية عن طريق الفم، مثل البيئة الحمضية في الجهاز الهضمي وتفكك الإنزيمات، وتناقش التقدم التكنولوجي المصمم لتجاوز هذه العقبات.

النتائج :تشمل التطورات الرئيسية تطوير الهلاميات الهلامية المتجاوبة مع الأس الهيدروجيني، وأنظمة التوصيل المعتمدة على الإبر الدقيقة، وحوامل الجزيئات الجديدة. تهدف هذه الابتكارات إلى حماية الأدوية من ظروف الجهاز الهضمي القاسية، وتعزيز امتصاص الأدوية، وتوفير الإفراج المنظم. على الرغم من هذه التقدمات، تظل التحديات مثل استقرار الأدوية، وتداول المخاط، واستهداف الجزيئات الكبيرة بشكل فعال، كبيرة.

الاستنتاج :شهدت أنظمة توصيل الأدوية عن طريق الفم تقدمًا كبيرًا، خاصة في التطبيقات البيولوجية. توفر الابتكارات مثل تقنيات التلبيس الدقيقة المتقدمة وأجهزة التوصيل الجديدة حلولًا واعدة لتحديات الإدارة عن طريق الفم. ومع ذلك، هناك حاجة إلى مزيد من البحث لمعالجة الحواجز التقنية والبيولوجية المتبقية، وتحسين استقرار الأدوية، وضمان توصيل فعال للجزيئات الكبيرة واللقاحات.

الكلمات المفتاحية :توصيل الأدوية عن طريق الفم، المنتجات البيولوجية، الهلاميات الهلامية المتجاوبة مع الأس الهيدروجيني، الإبر الدقيقة، حوامل الجزيئات، استقرار الأدوية، الحواجز الهضمية.