Exploring Recent Progress In Oral Drug Delivery Systems.

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Abstract:
This thorough talk covers all the nuances of oral drug delivery systems, from the current developments in microencapsulation technology to the critical role mucus plays in gastrointestinal physiology. The discussion starts out by outlining the various roles that mucus plays in the gastrointestinal tract, such as its barrier qualities and its part in mucosal immunity. It then explores the various drug absorption mechanisms, including paracellular and transcellular pathways, as well as the difficulties caused by tight junctions. A number of oral drug delivery systems are carefully analyzed, including intestinal patches, gastrointestinal microneedles, and particulate carriers like liposomes and micelles. The discussion goes on to discuss the potential for improved therapeutic efficacy of sustained drug delivery strategies, such as thiol-functionalized carriers and mucoadhesive hydrogels. Novelties in gastric-resident structures, like foldable rings with elastic properties and solvent-free microencapsulation technologies utilizing microfluidic devices, are emphasized as potentially effective approaches to surmount current drug delivery obstacles. The dynamic nature of oral drug delivery research and its potential to transform therapeutic interventions are highlighted in this thorough discussion.

Key words: oral drug delivery, gastrointestinal tract, mucus, microencapsulation, sustained release, mucoadhesion, microfluidics, gastric-resident architectures, drug absorption, tight junctions.

Introduction:
The main methods of delivering drugs are by intravenous (IV), intramuscular (IM), intranasal (IN), intradermal (ID)/transdermal, and oral delivery [1]. Furthermore, specific delivery methods such as ocular delivery have been developed to allow for targeted medication administration, hence reducing systemic side effects [1]. Different delivery methods face different obstacles to efficient drug transportation. Drug targeting, preservation, and therapeutic efficacy are all greatly aided by the incorporation of medications into delivery systems. An overview of various administration routes is given in this paper, with a focus on oral delivery systems because of their appeal. It outlines the main difficulties with these kinds of systems and looks at new developments that try to get beyond them. The drug's characteristics and the mode of absorption play a crucial role in determining which delivery strategy is best for maximizing bioavailability and effectiveness. For immunizations, for instance, IM and ID routes are usually recommended based on desired immune response mechanisms. On the other hand, because IN and oral vaccination systems have the ability to stimulate mucosal and systemic immune responses, they have attracted a lot of interest from the academic and industrial communities. By quickly injecting medications into blood vessels, intravenous (IV) administration produces the best bioavailability and fastest onset of effect of any delivery method by getting over physiological absorption obstacles. As a result, it is still the procedure of choice for urgent and acute cases, but non-invasive techniques are more appropriate for long-term treatment and delivery [2]. Bypassing the skin's first line of defense, the extensive vascularization of muscles makes it easier for drugs to be absorbed through intramuscular injection [3]. While the lack of the gastrointestinal (GI) environment is one advantage of intravenous (IM) delivery over oral administration, there are drawbacks as well, including needle anxiety, discomfort, incorrect needle disposal, and the requirement for medical professionals with specialized training. In addition, injecting directly into the bloodstream raises questions about potential side effects, which calls for close observation to reduce risks [4,5, 6].
Since most biopharmaceuticals, including vaccinations, are delivered via intramuscular (IM) injection, there are unique delivery problems associated with them [7]. This preference results from the restricted permeability of macromolecular biopharmaceuticals via non-parenteral routes across mucosal membranes and their vulnerability to protease degradation in the gastrointestinal (GI) tract [8]. Particularly in topical injections, mesoporous structures made of silica and polymers present intriguing approaches for drug preservation in biological settings and exact control over release kinetics [9,10,11]. However, due to lower immunogenicity and bioavailability, subcutaneous or intravenous (IV) injection may be a better option for peptide and protein administration than IM injection [12]. Even though IM administration is widely used in

medicine and might trigger immune responses through the creation of local depots, there are certain drawbacks, including the possibility of drug aggregation, particularly with peptides and proteins [13].

The transdermal method, which mainly uses intercellular, transcellular, and transappendageal channels, involves transferring drugs over epidermal layers and into the circulation [14]. Drug entrance via sweat ducts or hair follicles with associated sebaceous glands is facilitated by intercellular and transcellular transport pathways [15], whereas the transappendageal pathway involves drug entry through hair follicles [14]. Transdermal administration avoids gastrointestinal complications while providing stable plasma medication levels and a simple way to stop treatment in the event of an adverse reaction. Recent developments include the application of nanoparticles (NPs) on nano/micro-engineered needle patches to reduce the risk of bacteria [16] and the use of nanoimprint lithography to fabricate patches in order to satisfy market expectations. A deposition-etching process for flexible silicon nanoneedles was proposed by Kim et al. [17], which made it possible to successfully inject biomolecules into living tissues. The size restriction on medication molecules appropriate for transdermal distribution, which makes it challenging for large molecules (>500 Da) to pass through the stratum corneum, is still a major obstacle. Drug absorption can be improved by chemical enhancers or physical methods. Fatty acids, surfactants, terpenes, and solvents are used in the former to break down lipid structures and alter the microstructure of the stratum corneum [19, 20]. When formulating chemical enhancers, toxicity and skin irritation are important factors to consider. Although the mechanisms underlying these effects and enhancer interactions with the stratum corneum remain unclear, Karande et al. looked into the synergistic effects of enhancers and developed key criteria for generating new formulations [21].

By directly injecting drugs into veins, intravenous (IV) administration circumvents the biological, chemical, and physical obstacles that other delivery methods must overcome [22]. It is best used in emergency situations due to its guaranteed and instantaneous absorption, which allows for exact control over dosage and delivery speed—especially for medications with strict dosing criteria. However, there are dangers associated with IV administration, including thrombosis, circulatory overload, infection, and needle-related injuries [23, 24]. IV administration is commonly used for biopharmaceuticals, but it may not be the best option for vaccinations since it can be difficult to elicit adequate immune responses and does not provide a sufficient local antigen depot to activate long-term antibody production and innate immune responses [25]. Furthermore, IV administration's applicability for widespread immunization campaigns is limited by its complexity and safety issues.

Drugs are administered via the highly vascularized mucosal layer of the nose through intranasal (IN) medication delivery, which is especially important for neurological diseases that need access to the central nervous system (CNS) [26]. Because IN administration has fewer systemic effects than other approaches, it is ideal for treating local disorders. It does, however, confront physicochemical limitations linked to drug characteristics influencing absorption methods as well as physiological barriers as capillary barriers, nasal mucus, clearance mechanisms, and nasal metabolism [29]. Mucoadhesive microencapsulation methods have been created to improve medication bioavailability by the removal of mucus-associated barriers, such as thiolated chitosan-coated nasal microcapsules [27]. Notwithstanding obstacles like mucociliary clearance and discharge restricting the amount of time a drug can remain in the body, IN delivery has benefits like avoiding gastrointestinal issues, avoiding first-pass metabolism, and enabling quick drug action—all of which are especially helpful in emergency situations and the direct delivery of neurological drugs to the central nervous system.

The main site for inducing mucosal immunity in nasal vaccination is nasal-associated lymphoid tissue (NALT), where adaptive immunity—particularly IgA-mediated immunity—occurs at the mucosal layer and innate immunity is mediated by dendritic cells and macrophages [30]. As a result, the intranasal (IN) vaccine has the ability to promote systemic and mucosal immunity. However, physiological obstacles, most notably mucociliary clearance, prevent effective antigen delivery to the target region, requiring approaches to get over these obstacles. Furthermore, nasal vaccination is only possible with low dosage and low molecular weight chemicals due to the nasal cavity's limitations and the limited passageways beneath thick mucus. In order to address lung exposure, IN delivery systems must adhere to biosafety regulations, which include accommodating limited nasal openings and the complex nasal route geometry. Because of their excellent dispersion qualities, aerosol sprays are usually chosen for IN administration. However, continuing technical improvements are aimed at improving drug dispersion and modifying deposition and clearance behaviors through the integration of solid and liquid phases. However, restrictions arising from the physiology of the nasal passage and human anatomy continue to hinder clinical applications and delivery effectiveness. One of the biggest challenges for IN delivery systems is low bioavailability (<5%) [31].

Oral Route and Oral Administration:

Of all the various drug delivery routes, the oral route has attracted the most attention due to its unique benefits, which include easy administration, potentiated immune response, enhanced patient compliance, controlled and sustained delivery, suitability for solid formulations, and [32, 33, 34, 35, 36]. Furthermore, a viscous mucosal layer covering a large surface area (>300 m2) promotes drug adhesion and subsequent absorption [37, 38]. Furthermore, the shear pressures caused by the flowing stomach juices prevent from reaching medication molecules trapped in mucus [39]. The human gut's absorptive epithelium increases absorptive capacity because it is loaded with enterocytes from different segments, most notably microfold cells (M cells) that cover Peyer's patches [40,41,42,43,44]. However, the mechanisms involved in the absorption of oral drugs are quite complex. For oral medications to be absorbed in the stomach, small intestine, or colon, they must be soluble in gastric fluid. Four different paths can be used to absorb oral drugs: the transcellular pathway is the most common, followed by the paracellular, carrier-mediated transcellular, and facilitated transport pathways. Beyond the gut barrier, hepatic barriers post-entry into capillaries under the intestinal epithelium present challenges for

drug absorption and efficacy. In conclusion, because of their slow absorption and the various obstacles they face, oral medications are not appropriate for use in emergency situations.

While oral administration is the preferred route for administering small therapeutic molecules, the unfavorable conditions found in the gastrointestinal (GI) tract can compromise the integrity of active antigens through denaturation or degradation, which accounts for the lack of oral vaccines available on the market. However, research into oral vaccines is driven by the attraction of mucosal immunity, particularly that induced by nasal and oral routes [49]. Oral delivery also has additional benefits, such as convenience, which highlight its potential for widespread immunization campaigns. Peyer's patches, lymphoid follicles in lymph nodes, and antigen-presenting cells (APCs), which resemble nasal mucosal immunity, are examples of inductive sites in the GI tract. Variations in pH and enzyme activity between GI sites are the biggest obstacle to vaccine administration, as they prevent mucosal penetration and access to gut-associated lymphoid tissue (GALT) [50]. Moreover, mucosal interactions have the potential to cause structural changes in proteins and peptides [38], which calls for the creation of delivery systems and formulations that improve immunogenicity and therapeutic efficacy. The FDA has approved seven live oral vaccinations as of right now.

Research has concentrated on creating oral delivery methods in order to meet the growing demand for oral biopharmaceuticals. Particulate systems, intestinal patch systems, and microneedle capsules are examples of modern technology, albeit they are still in their infancy [51]. A unidirectional drug release depot similar to a microdevice attached to the intestinal wall is a feature of intestinal patch systems [52]. By physically puncturing the mucosa with microneedles, microneedle capsules improve drug molecule penetration. A recent study developed a pH-responsive technique to introduce microneedles into the mucosa [53]. The most common oral delivery system, particulate matter devices, have been investigated for encapsulating and directing different types of treatments. The majority of current technologies are still in the preclinical stage, which means further study is needed to establish clinical feasibility and solve present technical issues with oral drug delivery systems.

Challenges of Oral Drug Delivery:

The gastrointestinal (GI) tract serves as a conduit for the transportation and absorption of medications taken orally. Most medications enter the bloodstream and act throughout the body, but some only have local effects in the stomach. There are upper and lower segments of the GI tract. The mouth, throat, esophagus, stomach, and the first segment of the small intestine (duodenum) are all included in the upper GI tract. The lower GI tract consists of the cecum, colon, and rectum, as well as the remaining segments of the small intestine (jejunum and ileum) [54, 55]. Although there are segmental differences, the GI tract has a uniform architecture with smooth muscle cells encircling the lumen and embedded in layers of muscle, mucus, and submucosa [56]. Important for the transportation of food and medication molecules as well as gastrointestinal immunity, the mucosal layer that lines the inner side of the GI tract is made up of epithelial cells, lamina propria, and muscularis mucosae [54, 55]. Drug absorption is facilitated by the large absorption area and extended residence time in the small intestine; the ileum and jejunum are better at absorption than the duodenum [57,58].

Segment length, pH, mucus thickness, drug residence time, and bacterial diversity/population throughout segments are among the environmental variables that affect drug integrity and absorption [38,59,60]. Oral administration obstacles mostly fall into two categories: biological barriers and technical difficulties. Technical hurdles refer to difficulties in constructing oral delivery systems, whereas biological barriers include biological processes that denaturate medications taken orally or impede effective absorption. Developing unique qualities to overcome biological limitations or obstacles in scaling up and commercializing systems are examples of technical problems.

Any material that is consumed in the gastrointestinal (GI) tract comes into contact with three main biological environments: tissue, mucus, and lumen (internal space), all of which have the ability to interact with medication molecules. Lumen: The harsh acidic pH 1-2 conditions of the stomach act as the first biological barrier against medications taken orally. These conditions can denature or depurinate numerous molecules, hence significantly lowering their potency [61,62,63,64]. Pepsin and gelatinase are examples of gastric enzymes that further break down biopharmaceuticals. Drugs can be encapsulated in pH-responsive hydrogels to protect them from gastrointestinal enzymes and acidic surroundings. When certain environmental triggers are encountered, these hydrogels release their cargo, remaining intact in unfavorable circumstances. For instance, sensitive medications such as insulin are well preserved against gastric and intestinal enzyme fluids by pH-sensitive hydrogel microparticles (MPs) [65]. In a similar vein, protection against enzymatic conditions and gastric acidity has been proven via a pH-responsive microencapsulation device [66].

The duodenum, the main entrance to the small intestine, contains pancreatic and stomach enzymes, although for a variety of reasons these are not regarded as significant obstacles. First, in the jejunum and beyond, their concentrations drastically decrease [69]. Furthermore, by the mid jejunum, even purposefully administered pancreatic enzymes show a significant drop in concentration [70]. Second, the duodenum's short transit time for broken-down food reduces the possibility for drug degradation by enzymes [71]. Finally, by modifying the pKa of the carriers, the duodenum's pH, which is lower than that of later small intestine segments, enables the regulated release of medications [72].

Drug efficiency may be reduced by the lumen's exposure to osmotic and mechanical stresses, such as peristalsis and shear stresses from gastric juice flow, in addition to acidic and enzymatic degradation [32, 38]. Additionally, by shortening the duration of interaction between drug molecules and the epithelial layer, these mechanical stresses may impede absorption [67]. Biological agents are especially vulnerable to mechanical destruction, such as viruses, vaccines, and cells. Hydrogel characteristics like mechanical strength are important, even though microencapsulation can help address these problems. For example, hydrogel matrices have been reinforced with cellulose nanocrystals (CNCs) and hydroxyapatite, greatly

improving their mechanical properties [73]. Unfortunately, little is known about the reinforcing agent dispersion mechanisms in polymer matrices, which impact swelling, gelation, and degradation rates in addition to mechanical properties [74]. Notwithstanding these difficulties, adding CNCs to hydrogels has demonstrated remarkable gains in mechanical characteristics without the need for additional modification.

The GI tract's second compartment, mucus, interacts with everything that has been broken down. The entire GI tract is coated with this elastic, sticky, and viscous film that traps foreign molecules, particularly those that are hydrophobic, and prevents them from contacting the epithelial layer. Mucus, which is composed of water, mucin protein molecules, proteoglycans, carbohydrates, salts, bacteria, antibodies, and remains of cells, functions as an immune system component and barrier, a process referred to as mucosal immunity. The mucosal layer is made up of two different layers: an inner, firmly adhering layer and an outside, loosely adherent layer. Mucins are huge macromolecules that are crosslinked to produce the mucosal layer. Mucus has two roles: it hinders drug transition to submucosal tissue in the outer layer, and it facilitates medication absorption in the inner layer. Mouth medication delivery techniques that penetrate mucous membranes include mucopenetrating and mucoadhesive techniques. Mucolytic enzymes lower mucus viscosity, while mucopenetrating carriers regulate hydrophobicity/hydrophilicity to pass through mucus. Mucoadhesive carriers prolong drug transition time by taking advantage of mucus's protective qualities. However, continuous delivery is hampered by the short residence duration and variable thickness of mucus, which calls for more investigation [75].

The gastrointestinal (GI) tract absorbs medications or microparticles (MPs) that are taken orally based on their unique properties, which define the absorption sites and pathways. Absorption is facilitated by two main pathways: diffusion through the gaps between epithelial cells (paracellular route) and transcytosis by cells (transcellular route). The main extracellular biological barrier, tight junctions, regulate the paracellular absorption pathway and so restrict absorption. Because of their size and chemistry, hydrophobic molecules, nanoparticles, vesicles, and micelles prefer transcellular pathways, whereas hydrophilic small molecules prefer paracellular ones. However, the bulky polar head groups of lipid membranes impede passage across cell membranes. Enzymes and other cellular constituents may further break down drug molecules in the cytosol, lowering the medication's potency. The majority of medication compounds face difficulties because passive diffusion through intercellular pathways is restricted to substances smaller than a few nanometers. Lipid-based carriers and permeability enhancers, such as SNAC and PIP peptides, which dynamically modify endogenous mechanisms to open tight junctions and promote paracellular transition—particularly for peptide therapeutics—are two methods for getting beyond paracellular barriers. Tight junctions are still a significant challenge despite recent advancements because of our incomplete knowledge of the mechanisms underlying tissue permeability and the effects of different treatments [76].

Oral Delivery System Challenges:

Oral drug delivery devices fall into three primary categories: particulate carriers such as liposomes, micelles, and microparticles (MPs), and gastrointestinal microneedles. Mucoadhesive blankets called intestinal patches are affixed to the inside walls of the gastrointestinal tract. They provide a drug reservoir that enhances medication bioavailability by guarding against harsh conditions and luminal loss. They have limitations, such as short retention duration and separation from the lumen wall, despite their potential. Initially designed for transdermal distribution, gastrointestinal microneedles are currently being investigated for oral administration. They hold potential for delivering big macromolecules with enhanced bioavailability, but further research is necessary, particularly in clinical trials. Particulate carriers—micelles, liposomes, and MPs, among others—are frequently researched for oral administration because of their controllability and adaptability. For example, liposomes can encapsulate hydrophilic and hydrophobic medications, while micellar membranes can boost the solubility of hydrophobic pharmaceuticals and their penetration through tissues. MPs, which are stimuli-responsive materials derived from polymers or ceramics, present a number of issues, one of which is managing porosity to ensure effective drug delivery. A primary area of research in the subject is centered around achieving appropriate porosity, which is essential for the delivery of big macromolecules or cells as well as small medicinal molecules.

Maintaining a constant drug concentration in the bloodstream is crucial for effective treatment, as fluctuations can lead to toxicity or ineffective therapy. Sustained drug delivery, achieved through materials like positively charged hydrogels or thiol-functionalized hydrogels that attach to mucus, has been explored to extend delivery times. However, these approaches only slightly increase delivery duration due to the short turnover cycle of intestinal mucus. To address this limitation, recent gastric-resident architectures have been proposed. Traverso and Langer introduced the concept of large delivery architectures that exceed specific gates in the GI tract, such as the cavity before the anus or the pyloric sphincter. Zhang et al. developed an elastic, foldable O-ring made of hydrogels encapsulated in a degradable capsule, which, upon dissolution in the stomach, releases the ring into the stomach cavity. The drug-loaded segments of the ring gradually degrade, releasing the drug over several days. While this approach shows promise for prolonged drug delivery, concerns remain regarding potential obstruction of the GI tract and adverse effects, highlighting the need for further research to address these challenges.

Microencapsulation systems, particularly microparticles (MPs), are crucial in drug delivery, with solid and hollow MPs being two main categories. Traditional fabrication methods often involve direct contact between drug molecules and organic solvents, raising concerns about drug denaturation. Multiemulsion systems were developed to minimize this contact but faced challenges in efficiency and control. Microfluidic devices have emerged as a promising alternative, offering highly uniform MPs with minimal drug-solvent contact. However, low throughput remains a limitation. Another approach involves separate processes for MP fabrication and drug encapsulation, minimizing the risk of drug denaturation.

Methods such as coating solid spheres with polymers and subsequently removing the core have been explored, but loading efficiency is often limited. Recent innovations include fabricating hollow polymeric microspheres with single surface pores using solvent evaporation methods, enabling direct drug loading and subsequent closure of pores to protect the drug during stomach transition. These advancements hold promise for improving drug delivery efficiency and minimizing drug denaturation concerns.

Conclusion:

In conclusion, an extensive array of subjects pertaining to oral medication delivery methods were discussed in detail. The gastrointestinal (GI) tract's mucus, its makeup, and its function as a barrier and component of the immune system are all covered in the first section. The conversation then explores the difficulties involved in drug distribution, such as tight junctions and mucosal barriers, as well as the processes of drug absorption in the GI tract, including transcellular and paracellular pathways. The topic of oral drug delivery systems is discussed in further detail, covering intestinal patches, gastrointestinal microneedles, and particulate carriers such as liposomes, microparticles, and micelles. Every one of these distribution systems is analyzed with respect to its design, manufacturing processes, and possible uses. The discussion then turns to methods for sustained drug administration, emphasizing the significance of preserving steady drug concentrations in the bloodstream as well as the creation of hydrogels that are mucoadhesive and thiol-functionalized for extended drug release. Finally, new developments in microencapsulation technologies, fabrication techniques for microparticles, and gastric-resident architectures are explored. These include the creation of hollow polymeric microspheres with single surface pores for enhanced drug loading efficiency and the application of microfluidic technologies for consistent microparticle manufacture. All things considered, the discussion offers a thorough review of oral drug delivery methods, including their difficulties, developments, and prospective uses in the pharmaceutical industry.

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