



Emerging delivery platforms for Oro-mucosal administration of biopharmaceuticals: a critical update

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ABSTRACT

Sometimes drugs are injected straight into veins. This is known as Intravenous administration. The medication reaches the blood supply directly in this scheme, eliminating any chemical, physical, or biological barriers. Since the absorption of the drug is guaranteed and immediate, IV administration is the best route for emergency situations. Furthermore, this technique allows highly exact controls over the dose and pace of administration, making it the optimal solution for medications that need a strict dosing regimen. On the other side, the IV method has risks of infection from the injection site caused by the needle such as phlebitis, thrombosis, and circulatory overload. Intravenous administration is a common method for delivering biopharmaceuticals. Because the bioavailability of the medicine administered via IV is theoretically 100%, making this approach performs better than other delivery routes. However, it should be noted that IV administration is not the ideal route for the delivery of vaccines. This is due to the difficulties associated with inducing effective immune responses via IV administration since the IV route does not provide an adequate local depot of antigens to stimulate/activate the innate immune response and induce the long-term secretion of antibodies. As a great alternative, oro-mucosal drug delivery systems have advanced, and their importance has been growing vastly and used in clinical settings. This review summarizes them over the intravenous delivery system.

Keywords: Oral; mucosal; Drug Delivery; Intravenous; Bioavailability.

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INTRODUCTION

It is not applicable to implement a mass administration (such as nationwide vaccinations), due to the skills required for the practitioner, safety issues, and patients' compliance. Intranasal drug delivery entails the infusion of the drug into the highly vascularized mucosal layer of the nose to subsequently reach systemic circulation [1-6]. IN drug delivery is crucially significant for neurological diseases, where drugs are required to reach the

central nervous system (CNS) by bypassing the blood-brain barrier (BBB). In general, the IN route is preferred for local diseases due to its limited systemic effects compared to the other methods. The IN route also has its own specific physiological and physicochemical barriers. Capillary barriers, nasal metabolism, nasal mucus, and mucus clearance are aspects of physiological barriers.

Other parameters, like possible drug-mucus interactions, mucus viscosity, and PH may affect drug diffusion and absorption during IN delivery. Mucoadhesive microencapsulation methods have now been designed to overcome the mucus-associated barriers to IN administration and to increase the bioavailability of medicines delivered nasally. For instance, Nanaki et al., coated nasal microcapsules using thiolated chitosan to improve the mucoadhesion system, both chemically (disulfide bonds) and physically (electrostatic attractions) [7-11]. Moreover, it has to be emphasized that even if the carriers form a strong bond or binding with the mucus, the mucociliary clearance and discharge significantly restrict the drug residence time [12-19]. The physicochemical barriers significantly impact the drug's molecular weight, lipophilicity, and degree of ionization, which also determine the absorption mechanisms [20-25]. Although several challenges, IN is an attractive route for the delivery of a number of medicines. It minimizes first-pass metabolism and

Gastrointestinal problems. Due to its considerable absorption rate, IN is an applicable method for emergency cases and rapid drug action. Neurological drugs especially can be transported directly to the CNS through the IN route. The nasal-associated lymphoid tissue (NALT) is the principal target for inducing mucosal immunity in nasal vaccination. Innate immunity is achieved by macrophages and dendritic cells, and adaptive immunity at the mucosal layer is induced by IgA [26-28]. As a result, IN vaccination can stimulate mucosal as well as systemic immunity. Therefore, physiological barriers, particularly mucociliary clearance, must be addressed appropriately for effective antigen delivery to the target site. Furthermore, due to the limitations of the nasal cavity, as well as the narrow passages beneath the thick mucus, nasal vaccination is only permitted for small dosages and low-weight molecular compounds. IN delivery devices must be adequate for limited nasal openings and the complicated geometry of the nasal route in order to meet biosafety criteria. On top of that, lung exposure should be properly addressed in these systems. Aerosol sprays are often preferred for intranasal administration among the many physical states of medications (aerosol sprays, gels, droplets, or powders). New methods are continually being developed to increase medication dispersion and change deposition and clearance behavior by mixing both liquid and solid phases. However, the human anatomy as well as the physiology of the nasal cavity and passage still limit clinical applications and delivery efficiency.

Oro mucosal dosage form absorption and activity

The oral route has received the most attention among the many drug delivery routes because of its unique advantages, which include continuous and controllable delivery, ease of administration, feasibility for solid formulations, patient compliance, and an intensified immune response in the case of vaccines [29-34]. Furthermore, a huge surface area (>300 m²) coated by a viscous mucosal layer facilitates the way for medication attachment and then absorption [35-40]. Additionally, drug molecules entrapped in mucus are shielded from shear forces induced by flowing gastrointestinal fluids [41-46]. The human intestinal epithelium is extraordinarily absorbent because of the large number of enterocytes in various parts of the intestine, particularly microfold cells (M cells) covering the Peyer's patches, and the lymphoid portion of the small intestine [47-54]. Moreover, the absorption mechanism of oral medicines is more complex when compared to other routes. Oral drugs need to be soluble in gastric fluid so they can be absorbed in the stomach, the small intestine, or the colon.

Recent Delivery trends in oral routes

Drugs taken orally can be absorbed in four ways: transcellular, facilitated transport, paracellular,

and carrier-mediated transcellular. The most significant of these mechanisms is the transcellular route. The obstacles to medication absorption or efficacy are not limited to the barriers met in the gut, but also include the hepatic barriers when they reach the vessels underneath the intestinal epithelium. To summarise, oral medications are not appropriate for an emergency situation because of their sluggish absorption and the various levels of barriers they must overcome. Although the oral route is the most desirable administration method for small therapeutic molecules, there are not so many oral vaccines on the market due to the harsh conditions along the GI tract which can degrade/denature active antigens. However, the attraction of mucosal immunity, which appears to be induced by oral and nasal routes, promotes the study of oral vaccines [55-60]. Besides, the convenience and other advantages of oral delivery make it a very promising strategy for mass vaccination programs. The inductive sites in the GI tract consist of Peyer's patches, lymphoid follicles in lymph nodes, and antigen-presenting cells (APCs). Intestine mucosal immunity is similar to that of nasal mucosal immunity. The main barrier to vaccine delivery is the change of pH in different sites in the GI tract and various enzymes, making it hard to permeate the mucus and reach the inductive site in gut-associated lymphoid tissue (GALT) [61-64]. Additionally, the mucosa may lead to the structural change of proteins and peptides due to various possible interactions [65-70]. Hence, delivery vehicles and formulations should be developed to gain stronger immunogenicity to meet the required therapeutic efficacy. Currently, seven live oral vaccines have already been approved by FDA. To accommodate the growing demands for biopharmaceutical oral pharmaceuticals, researchers have concentrated on creating devices for oral delivery. The latest devices include microneedle capsules intestinal patch systems, and particulate systems, all of which are still in the early stages of development [71-75].

To utilize MSNs as well as HNTs in drug-delivery systems, their pore gates must be sealed with a third substance called a gatekeeper or cap. Stimuli-responsive hydrogels have been mainly investigated as sealing materials to confer target-specificity to MSNs [76-77]. Different types of stimuli (i.e., magnetic, light, thermal, and pH) have been employed to date for MSN systems. Stimuli-responsivity in this microencapsulation scheme can be implemented through two main approaches: (1) Cleavable covalent bonding/crosslinking between the carrier and the drug in response to stimuli, such as the cleavable bonding at pH values below the plasma pH, and (2) functionalization of the surface or coating of the channels, which can switch conformation based on the surrounding properties and stimuli-responsive caps. As an example, doxorubicin was conjugated to the interior walls of the channels in MSNs through

pH-sensitive hydrazine bonds, which can prevent any untimely release of the drug. That is, upon being taken up into the cell through endocytosis, the acidic conditions of the endosomal/lysosomal environment can trigger the release of drugs due to the protonation of the bonding [78]. Another example includes light-responsive MSNs, made by Mekaruru et al. using photoactivated azobenzene, which triggered release upon excitation by an external source of light [79-80]. These light-responsive MSNs are among the most common carriers used for cancer therapies.

CONCLUSION

The intestinal mucosal patch systems are based on a unidirectional drug release depot, which is similar to a microdevice adhered to the intestinal wall. By directly piercing the mucosa with microneedles, the microneedle capsule enhances the rate of drug molecule penetration. A recent study developed a method to inflate a microneedle into the mucosa by responding to the change in pH. In general, the current technologies are still in the preclinical stage. As a result, additional research efforts must be dedicated to resolving the present technological obstacles of oral drug delivery systems and proving the practicability of clinical use. The Challenges of oromucosal medications are carried and absorbed in the gastrointestinal tract, which is shaped like a conduit. Some drugs have local effects in the gut, while most of them are sent to the bloodstream in systemic circulation to act in other parts of the body that needs to be explored and reported

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