Clinical perspective of advances in oral dosage form delivery systems

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ABSTRACT

The primary drug delivery methods are intravenous (IV), intramuscular (IM), intranasal (IN), intradermal (ID), transdermal and oral administration. Other routes, such as ocular delivery, have also been developed for localized, site-specific drug administration without unwanted systemic side effects. Each mode of administration poses particular barriers in terms of drug delivery. Furthermore, medications can be integrated into delivery devices, which significantly contributes to therapeutic efficacy, drug preservation, and targeting. We initially present the overview of the many administration methods in this review before concentrating upon oral delivery systems as being the most appealing route. We explain the main challenges associated with such methods and review the most recent solutions developed to address them.

Keywords: Oral delivery, Tablets, Capsules, Pharmaceutical Technology, Pharmacokinetics.

INTRODUCTION

The absorption mechanisms as well as the nature of the drug are the fundamental factors that determine the appropriate delivery systems for achieving the highest bioavailability and effectiveness. For instance, IM and ID administration is usually the preferred vaccination routes, depending upon the desired immune response mechanisms. On the other hand, researchers from both academia and industry have shown great interest in IN and oral vaccination systems, since these routes can induce both systemic and mucosal immune responses. In IV administration, the drug is rapidly injected into blood vessels through needles, and a high concentration of the drug is able to bypass the physiological barriers against drug absorption, providing the highest bioavailability and the fastest effect among all delivery routes. As a result, parenteral administration has been the recommended route for urgent and acute responses, whereas non-invasive techniques are better suited for chronic delivery and long-term therapy. The ample quantity of blood vessels in muscles covers the way for the absorption of medications administered via injecting intramuscularly (IM). The intramuscular route avoids the body's initial barrier of defense (skin). In comparison with oral administration, drugs administered through the IM route avoid the gastrointestinal (GI) environment. However, the injection can cause significant problems, including needle-associated phobia and pain, unsafe needle use and improper disposal, the need for trained healthcare personnel, muscle atrophy, and injuries to bones and nerves. Furthermore, the administration of medications directly into the bloodstream via IM raises concerns about necessitating constant close monitoring to reduce side effects. Biopharmaceuticals such as vaccines are of particular interest in drug delivery because of their specific challenges. The majority of the available vaccines are administered through IM injection. This is mainly due to the poor permeability of macromolecular biopharmaceuticals across the mucosal layer in the non-parenteral route and the destructive effects of proteases in the GI tract. Polymer and Silica mesoporous nanostructures may also be utilized to successfully preserve drugs in a variety of biological environments and precisely regulate their release behavior in topical injections. However, it should be noted that IM administration is not the ideal delivery route for peptides and proteins, compared to subcutaneous or IV injections, mostly due to the reduced immunogenicity and bioavailability attained with...
intramuscular administration \[27\]. Although IM vaccination is widely used commercially and the immune response in this system can be easily induced by the local depot at the injection site, this route is not the best choice for the delivery of peptides/proteins due to the possible aggregation of the drug \[28\]. The transdermal method is used to deliver medications through the layers of the skin to the blood circulation system \[29\]. In this scenario, drug absorption is mostly accomplished via transcellular, intercellular, and transappendageal paths. Permeation via the stratum corneum is enabled through intercellular and transcellular transporters \[30\].

**Delivery and absorption mechanism**

The drug enters the transappendageal pathway through the hair follicles or the sweat ducts with their associated sebaceous glands \[31\]. Additionally, the oral route’s issues with metabolism and the GI environment are avoided by using the transdermal method. However, it can offer a constant drug plasma level and the convenience of drug discontinuance in the event of adverse side effects. Recently, nanoparticles (NPs) were successfully employed on nano/micro-engineered needle patches to minimize the bacterial risks associated with transdermal delivery techniques \[32\]. Nanoimprint lithography has also been proposed as a fabrication technique for these structures to address commercial requirements. Kim et al. have developed a novel deposition-etching procedure for the production of pliable silicon nanoneedles in order to resolve structural mismatches and optical inconsistencies among Si needle wafers as well as soft tissues. \[33\]. The patches created using this technology successfully injected biomolecules into live tissues. Nonetheless, the most significant challenge associated with transdermal administration is the restriction on the size of the drug molecules that can be successfully delivered. It is challenging for larger molecules (>500 Da) to penetrate through the stratum corneum. Additionally, the drugs are required to be soluble, so they can cross the outermost skin barrier \[34\]. To increase drug absorption levels in the transdermal delivery route, chemical enhancers (concerning the delivery of small molecules) and physical techniques (concerning the delivery of macromolecules) have been developed.

**Co-Delivery Systems** Although the co-delivery of drugs is not one of the core challenges associated with delivery systems, the administration of different drugs at the same time can play crucial roles in treatment efficacy in many cases. Delivering multiple drugs to target different sites at the same time can significantly reduce treatment time and the risk of failure \[35-38\]. Chemotherapy provides an example of co-delivery and its importance \[39\]. As another example, insulin delivery systems may cause a drop in the release of insulin due to frequent administration of the drug. The co-delivery of insulin and cyclic adenosine monophosphate (cAMP) was proposed to enhance the secretion of further insulin by activating the Ca2+ channels in the beta cells of the pancreas \[40-44\]. It is thus important to develop co-delivery systems for the encapsulation and delivery of multi-target drugs. A straightforward solution for co-delivery is the simultaneous administration of different drugs in separate delivery carriers \[45-50\]. Another solution is the concurrent encapsulation of different drugs in micelles, liposomes, or MPs. The implementation of this idea dates back to 2011 when an anticancer drug (MEK inhibitor PD0325901) and a therapeutic gene (McIl-specific siRNA (siMcIl)) were concurrently loaded into N0, N4-dioleylglutamate-containing cationic liposomes \[51-57\]. This novel co-delivery approach significantly improved anticancer efficacy in vitro and in vivo. Cao et al. also simultaneously incorporated adenovirus encoding for murine interleukin-12 (AdS) and paclitaxel (PTX) into anionic liposomes and performed in vitro/in vivo analyses, confirming that their co-delivery system (AL/AdS/PTX) is an effective platform for treating melanoma \[58-59\]. Oral vehicles depending on SiO2 are also among the most often utilized delivery vehicles, particularly for co-delivery \[60-64\]. Mesoporous silica nanoparticles (MSNs) and halloysite nanotubes (HNTs) are the principal examples of SiO2 structures investigated for such applications. HNTs are naturally forming structures, available in sufficient amounts in North America, China, and New Zealand, making them a valuable candidate material in the pharmaceutical industry by meeting the requirements for scaling up and commercialization. MSNs have received substantially more attention as drug carriers than HNTs, despite the fact that their manufacture is more time-consuming and costly, mostly due to their larger interior space and higher loading capacity \[65-70\]. MSNs are nanoparticles made of silica with high chemical stability, a porous structure, and the ability for surface modification/-decoration \[71-80\].

**CONCLUSION**

The enhancement of physical skin permeability involves electrically aided techniques including electroporation, iontophoresis, and sonophoresis. Chemical enhancers include fatty acids, surfactants, terpenes, and solvents, which improve skin permeability by disrupting the highly ordered lipids and modifying the stratum corneum microstructure. However, toxicity and skin irritation are the major concerns to consider when developing chemical enhancer formulations. Others investigated the synergistic effects of several enhancers using a library of over 4000 binary formulations and discovered some essential rules for developing new formulations. While these rules are well-known and widely accepted, the mechanisms behind such potential synergistic effects and the interactions each individual chemical enhancer might well have with
other stimulants or the stratum corneum are still unclear in clinical settings.

REFERENCES


