Methodologies for Drug Delivery

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Introduction

Delivering medicines to patients in a safe, effective and compliant way is a major challenge in today's health care (1). Pills and injections comprise the most commonly used modalities for administering drugs. Pills are generally accepted as a convenient mode of drug delivery, however, their use is limited to small molecules (2). Macromolecular drugs such as peptides and proteins cannot be taken orally and have to be administered via injections. Furthermore, many drugs, regardless of their mode of administration, need to localize in specific diseased tissues and systemic administration of these drugs to healthy tissues can be toxic (3). Collectively, these challenges have made conversion of potent biomolecules into actual medical therapies very challenging. This challenge, which led to the foundation of the field of drug delivery some time ago, has now become a significant component of overall drug development process. This article focuses on some of the key developments in the field of drug delivery, especially those that deal with the development of painless and patient-friendly alternatives to injections for delivery of macromolecules.

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Need for better Methods of Drug Delivery

Needles and syringes are the most commonly used method for administering macromolecular drugs into humans. An estimated 12 billion injections are given annually worldwide (4). Despite their common use, needles have several limitations including needle-phobia (5), and accidental needle sticks (6). Additionally, there is an increasing concern over unsafe use of needles, as exemplified by an overwhelming number of HIV, hepatitis C, and hepatitis B infections that are thought to originate each year from re-use of needles and syringes (7). Not surprisingly, development of needle-free methods of drug delivery has received significant attention in recent past (8).

Drug administration through body surfaces such as skin and mucosal membranes of the mouth, nose, and lungs represents a viable alternative to needle-based methods. However, these surfaces offer significant barriers to drug entry into the body. Accordingly, breaching these barriers in a safe and effective way is one of the major goals of drug delivery research. This article provides an overview of the past efforts, current status and future perspective, particularly with an emphasis on transdermal and oral drug delivery.

Transdermal Drug Delivery

Transdermal delivery includes placement of drugs on the skin in the form of a patch, cream or lotion wherein the drug permeates across the skin and enters blood circulation. Key advantages of transdermal delivery include easy accessibility of skin which aids in

patient compliance, avoidance of gastrointestinal tract and ability to achieve sustained release over longer time periods (9). However, skin is a highly effective barrier of the human body (10), which restricts the applications of transdermal drug delivery to a handful of low molecular weight drugs. Therefore, there is a need for the development of technologies to enable transdermal delivery of macromolecular drugs in a controlled and reproducible fashion.

Technologies used by transdermal devices can be classified into passive or active methods based on whether an external source of energy is used for skin permeation enhancement. Passive methods include use of chemical enhancers, micelles, liposomes or peptides (11-15). Examples of chemical enhancers used for transdermal drug delivery include fatty acids, fatty esters, solvents and surfactants (16). Collectively, they increase transdermal transport of drugs by enhanced drug solubility, increased partitioning into the skin, fluidization of the crystalline structure of skin's topmost layer, and dissolution of the skin lipids. Chemical methods are relatively easy to incorporate into transdermal patches and can be calibrated to deliver various pre-determined amounts of drug by changing the application area. However, passive methods cannot be used for actively controlling the drug dose.

An increasing number of researchers are now exploring transdermal devices with active mechanism for skin permeation. These methods include microneedles, jet injectors, ultrasound, iontophoresis, and electrophoresis among others (11, 17-24). Microneedles comprise arrays of micrometer sized shallow needles that penetrate only

into superficial layers of skin thereby avoiding pain associated with standard hypodermic needles (25). In contrast, jet injectors deliver a high velocity liquid jet stream into skin, delivering drugs into various skin layers depending on the jet parameters (26). Ultrasound enhances skin permeability due to cavitation, which temporarily disrupts skin structure (27, 28). Iontophoresis and electroporation use electric fields to alter the skin structure and/or provide additional driving force for drug penetration through skin (29, 30). Active methods can be controlled in real time by varying appropriate parameters. Also, the device and application parameters can be adjusted to better match patient's skin properties.

While many technologies have been individually shown to enhance transdermal drug transport, their combinations are often more effective compared to each of them alone (31). A combination of two or more technologies may not only increase the total enhancement, but may also potentially increase their safety. Understanding the synergies between various technologies and selecting the right combinations represents a large opportunity which still generally remains untapped.

Over the last decade, significant new insights have been developed into structural organization and barrier formation of the skin. Skin, which has previously been looked upon primarily from the perspective of a barrier, is now known to be a smart material that controls its own structure and function in response to the environment (32). This new view and knowledge need to be incorporated into future development and evaluation of transdermal technologies.

Oral Delivery

Oral delivery of macromolecules has been a major challenge due to low oral bioavailability of proteins and peptides (2). Proteins are susceptible to enzymatic degradation in the intestinal lumen. In addition, they possess low permeabilities across the intestinal epithelium. Consequently, the scientific community has made a major thrust in recent years to overcome these obstacles to oral delivery through the development of a large number of new and innovative drug delivery techniques (33-40). These methods include the use of enzyme inhibitors, permeation enhancers, mucoadhesive polymers, chemical modification of drugs, targeted delivery, and encapsulation approaches.

Enzyme inhibitors are used to counteract the natural functions of the enzymes of the gastrointestinal tract meant to break down ingested proteins. Many studies have been performed in which inhibitors were co-administered with a drug (41), however, these strategies have been seldom successful unless absorption enhancers are used in combination. Permeation enhancers have also been used to overcome the challenges in

oral drug delivery along the same lines as transdermal drug delivery (42). Examples of permeation enhancers include surfactants, fatty acids, and bile salts. These enhancers either disrupt the epithelial membrane of the intestine or loosen the tight junctions between epithelial cells. While numerous studies have demonstrated that certain enhancers can be very potent delivery aids, safety concerns abound (43).

Mucoadhesive strategies have also been used to localize drugs to a small, defined region of the intestine through attractive interactions between the carrier and the intestinal epithelium. This localization results in a high concentration gradient of the drug across the epithelial barrier, which leads to improved drug bioavailability. Additionally, a strong adhesion force prolongs the residence time of the dosage form at the site of drug absorption. This reduces the dosing frequency, which, in turn, increases the patient compliance of the drug delivery system. Certain mucoadhesive polymers such as polycarbophil and chitosan derivatives have favorably shown to simultaneously act as permeation enhancers and enzyme inhibitors (35, 36).

Encapsulation technologies provide another alternative for stabilization and oral administration of drugs. Commercially available pH-sensitive polymers make it possible to target particular regions of the intestine (e.g., jejunum and colon) for drug delivery. Enteric coatings made from these pH-sensitive polymers enable drug delivery devices to pass through the acidic environment of the stomach unscathed and rapidly dissolve in the intestine. Studies to evaluate these polymers for targeted oral delivery are ongoing in various laboratories (33, 34). Encapsulation strategies of various forms including

microparticles (44), nanoparticles (45), and liposomes (46) have been developed. These strategies can protect proteins from enzymatic degradation in the intestine and/or can facilitate protein uptake across the epithelium (42).

Conclusions

Novel, painless and friendly methods of drug delivery represent an unmet need in the field of health care. Discoveries over the last decade have proven the feasibility of using several methodologies for enhancing drug delivery through skin and other mucosal surfaces. These methods have shown promise in delivering several molecules including macromolecules such as insulin and vaccines. With a diverse set of engineering tools at our hand, the future of drug delivery looks brighter than ever. The challenge now lies in converting these discoveries into useful products.

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