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Recent Trends in Dermal and Transdermal Drug Delivery Systems: Current and Future Prospects

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Transdermal patches delivers drug across skin to the circulatory system to achieve therapeutic effects or to provide local effect of drugs. As one of the fastest growing drug administration routes, it has several advantages compared to other traditional delivery methods: controlled release rate, more stable plasma concentration, noninvasive administration, less frequent dosing, and simple application without professional medical aids. The protective function of human skin imposes physicochemical limitations to the type of permeant that can traverse the barrier. For a drug to be delivered passively via the skin it needs to have adequate lipophilicity and also a molecular weight <500 Da. These requirements have limited the number of commercially available products based on transdermal or dermal delivery. Various strategies have emerged over recent years to optimize delivery and these can be categorized into passive and active methods. The passive approach entails the optimization of formulation or drug carrying vehicle to increase skin permeability. Passive methods, however do not greatly improve the permeation of drugs with molecular weights >500 Da. Magnetophoresis is a method of enhancement of drug permeation across biological barriers by the application of magnetic field. The general acceptability of transdermal products by patients is very high, which is also evident from the increasing market for transdermal products. The transdermal drug delivery market, worth $12.7 billion dollars in 2005, is expected to reach $32 billion in 2015.

Keyword: Dermal and Transdermal, Analgesic activity, adequate lipophilicity.

1. Introduction

Novel drug delivery is geared towards developing friendly dosage forms of various formulations with the ultimate aim of increasing their dosing convenience to the patient. The NDDS may involve a new dosage form e.g., from thrice a day dosage to once a day dosage form or developing a patch form in place of injections.The potential of transdermal drug delivery systems has been demonstrated in recent years with the approval of several medicines for use by patients who are unable to use conventional dosage routes, like oral administration or injection. To enhance the TDDS (Transdermal Drug Delivery System) potential to include other drug candidates, many researchers have been exploring enhancement approaches to increase the permeability of various drugs through the skin. Recently, physical enhancement systems are being reported as having big potential by many researchers. In particular, iontophoresis is a very attractive way of delivering ionized drugs by the application of an electric field to the skin. This has been marketed with some topical and systemic drugs (lidocaine and fentanyl). Sonophoresis is also an attractive method to deliver a drug through the skin using ultrasound. Besides these technologies, various physical approaches are under study. Such technologies can be expected to deliver not only small MW compounds but also macromolecules like peptides. In this article, after looking back through the history of TDDS

development, I would like to summarize with new physical and chemical approaches and outline of the new trend of TDDS development with those enhancement system.Transdermal drug delivery has made an important contribution to medical practice, but has yet to fully achieve its potential as an alternative to oral delivery and hypodermic injections. First-generation transdermal delivery systems have continued their steady increase in clinical use for delivery of small, lipophilic, low-dose drugs. Second-generation delivery systems using chemical enhancers, non-cavitational ultrasound and iontophoresis have also resulted in clinical products; the ability of iontophoresis to control delivery rates in real time provides added functionality. Third-generation delivery systems target their effects to skin's barrier layer of stratum corneum using microneedles, thermal ablation, microdermabrasion, electroporation and cavitational ultrasound. Microneedles and thermal ablation are currently progressing through clinical trials for delivery of macromolecules and vaccines, such as insulin, parathyroid hormone and influenza vaccine. Using these novel second- and third-generation enhancement strategies, transdermal delivery is poised to significantly increase impact on medicine.

2. Different Technique of Transdermal Delivery System

Innovations in technologies continue to occur at a positive rate, making the technology a fertile and vibrant area of innovation, research and product development. In the present study, various new development in the field of TDDS.

2.1 Iontophoresis

Iontophoresis passes a few milliamperes of current to a few square centimeters of skin through the electrode placed in contact with the formulation, which facilitates drug delivery across the barrier. Mainly used of pilocarpine delivery to induce sweating as part of cystic fibrosis diagnostic test. Iontophoretic delivery of lidocaine appears to be a promising approach for rapid onset of anesthesia.

2.2. Electroporation

Electroporation is a method of application of short, high-voltage electrical pulses to the skin. After electroporation, the permeability of the skin for diffusion of drugs is increased by 4 orders of magnitude. The electrical pulses are believed to form transient aqueous pores in the stratum corneum, through which drug transport occurs. It is safe and the electrical pulses can be administered painlessly using closely spaced electrodes to constrain the electric field within the nerve-free stratum corneum.

2.3. Application by Ultrasound

Application of ultrasound, particularly low frequency ultrasound, has been shown to enhance transdermal transport of various drugs including macromolecules. It is also known as sonophoresis. Katz et al. reported on the use of low-frequency sonophoresis for topical delivery of EMLA cream.

2.4. Use of Microscopic Projection

Transdermal patches with microscopic projections called microneedles were used to facilitate transdermal drug transport. Needles ranging from approximately 10-100 µm in length are arranged in arrays. When pressed into the skin, the arrays make microscopic punctures that are large enough to deliver macromolecules, but small enough that the patient does not feel the penetration or pain. The drug is surface coated on the microneedles to aid in rapid absorption. They are used in development of cutaneous vaccines for tetanus and influenza.

Various other methods are also used for the application of the transdermal patches like thermal poration, magnetophoresis, and photomechanical waves. However, these methods are in their early stage of development and required further detail studying.

2.5 Microneedles for Transdermal Drug Delivery:

Drugs with poor oral bioavailability usually are administered by hypodermic injection, which causes pain, poor patient compliance, the need for

trained personnel, and risk of infectious disease transmission. Transdermal (TD) delivery provides an excellent alternative, but the barrier of skin's outer stratum corneum (SC) prevents delivery of most drugs. Micrometer-scale microneedles (MNs) have been used to pierce animal and human cadaver skin and thereby enable TD delivery of small molecules, proteins, DNA, and vaccines for systemic action.

2.6 Advantages:

Delivers significant benefits compared to injection:

- Improved delivery efficiency of some drugs and vaccines
- Quicker onset of action for some drugs
- Potential to reduce drug costs by using less drug to achieve similar efficacy
• Potential to generate unique pharmacokinetic profile, difficult for competitive products to match
• Helps improve compliance compared to injection, based on the minimal discomfort associated with application and ease of self-administration
• Potential to reduce or eliminate side effects associated with other dosage forms
• Manufacturing expertise to meet your needs from clinical supplies to commercial scale.

2.7 Challenges and Opportunities In Dermal/Transdermal Delivery

Transdermal drug delivery is an exciting and challenging area. There are numerous transdermal delivery systems currently available on the market. However, the transdermal market still remains limited to a narrow range of drugs. Further advances in transdermal delivery depend on the ability to overcome the challenges faced regarding the permeation and skin irritation of the drug molecules. Emergence of novel techniques for skin permeation enhancement and development of methods to lessen skin irritation would widen the transdermal market for hydrophilic compounds, macromolecules and conventional drugs for new therapeutic indications. As evident from the ongoing clinical trials of a wide variety of drugs for various clinical conditions, there is a great future for transdermal delivery of drugs.Delivery of drugs through the skin has been an attractive as well as a challenging area for research. Advances in modern technologies are resulting in a larger number of drugs being delivered transdermally including conventional hydrophobic small molecule drugs, hydrophilic drugs and macromolecules. Transdermal systems are a desirable form of drug delivery because of the obvious advantages over other routes of delivery. Transdermal delivery provides convenient and pain-free self-administration for patients. It eliminates frequent dosing administration and plasma level peaks and valleys associated with oral dosing and injections to maintain a constant drug concentration, and a drug with a short half-life can be delivered easily. All this leads to enhanced patient compliance, especially when long-term treatment is required, as in chronic pain treatment and smoking cessation therapy. Avoidance of hepatic first-pass metabolism and the GI tract for poorly bioavailable drugs is another advantage of transdermal delivery. Elimination of this first-pass effect allows the amount of drug administered to be lower, and hence safer in hepato-compromised patients, resulting in the reduction of adverse effects. Transdermal systems are generally inexpensive when compared with other therapies on a monthly cost basis, as patches are designed to deliver drugs from 1 to 7 days. The other advantage of transdermal delivery is that multiple dosing, on-demand or variable-rate delivery of drugs, is possible with the latest programmable systems, adding more benefits to the conventional patch dosage forms.

2.8 Iontophoresis: A Potential Emergence of A Transdermal Drug Delivery System

The delivery of drugs into systemic circulation via skin has generated much attention during the last decade. Transdermal therapeutic systems propound controlled release of active ingredients through the skin and into the systemic circulation in a predictive manner. Drugs administered through these systems escape first-pass metabolism and maintain a steady state scenario

similar to a continuous intravenous infusion for up to several days. However, the excellent impervious nature of the skin offers the greatest challenge for successful delivery of drug molecules by utilizing the concepts of iontophoresis. The present review deals with the principles and the recent innovations in the field of iontophoretic drug delivery system together with factors affecting the system. This delivery system utilizes electric current as a driving force for permeation of ionic and non-ionic medications. The rationale behind using this technique is to reversibly alter the barrier properties of skin, which could possibly improve the penetration of drugs such as proteins, peptides and other macromolecules to increase the systemic delivery of high molecular weight compounds with controlled input kinetics and minimum inter-subject variability. Although iontophoresis seems to be an ideal candidate to overcome the limitations associated with the delivery of ionic drugs, further extrapolation of this technique is imperative for translational utility and mass human application.

2.9 Selection Criteria For Drug Candidate

Transdermal route of drug administration has certain inherent difficulties that make it unsuitable for a large number of drugs. The selection of suitable candidates is an important step for success of transdermal research

Ideal characteristic drug should possess for the successful delivery through this approach:

1. A TDDS should not cover an area more than 50 cm^2 and the daily dose is of order of a few mg.
2. The effective concentration of the drug should be low, presumably in the ng/ml.
3. The half life ($t_{1/2}$) of the drug should be short.
4. The active ingredients should not cause any skin toxicity or irritation.
5. As the diffusion of drug through polymer as well as skin is dependent on molecular size, the drug of low molecular size is preferred.
6. The drug should have a low melting point so that it acts on normal body temperature.
7. Drugs, which degrade in the GI tract or/are inactivated by hepatic first-pass effect, are suitable candidates for transdermal delivery.
8. Tolerance to the drug must not develop under the near zero-order release profile of transdermal delivery.
9. The candidate drug should have adequate hydrophilic and lipophilic balance to negotiate the lipid barrier of stratum corneum before being partitioned into the aqueous viable tissue.

2.10 Future Direction of TDDS

Expanding the use of novel permeation enhancement techniques with macromolecules and other conventional molecules for a wider range of indications is highly desirable for the transdermal industry. Physical enhancement methods afford substantial improvement in the rate of delivery of therapeutic agents across skin. Currently, a variety of them are undergoing extensive investigation and new device-based TDS can be expected in the near future. One can also expect the first transdermal prodrug product to emerge on the market in the near future. Novel prodrugs would not only help to reach the therapeutic levels for some drugs, but may also help alleviate skin irritation.The incidence and significance of skin irritation reactions will decrease with the increasing availability of physical permeation enhancement methods and new breakthroughs in topical drug formulations, such as liposomes, microemulsions, nanoparticles and evaporating gels. Breakthroughs in chemical permeation enhancer analogs showing significant improvements in limiting cutaneous irritation show promise for the development of safe chemical enhancers and should be further examined in the future

2.11 Clinical Application

2.11.1 Dentistry

Dentistry, probably to an even greater extent than physical therapy, has used iontophoresis with patients prior to oral surgical procedures.

1. Treatment of hypersensitive dentin (e.g. in teeth sensitive to air and cold liquids) using negatively charged fluoride ions;
2. Treatment of oral ulcers ("canker sores") and herpes orolabialis lesions ("fever blisters") using negatively charged corticosteroids and antiviral drugs, respectively; and
3. The application of local anaesthetics to produce profound topical anaesthesia, as is done in some physical therapy applications.

2.11.2 Dermatology

Iontophoresis has many uses in the field of dermatology. Except for the use of lidocaine for anaesthesia and the treatment of patients with hyperhidrosis, most uses of iontophoresis in dermatology have largely been abandoned. Iontophoresis with tap water or anticholinergic compounds has been used for the treatment of patients with hyperhidrosis of the palms, feet, and axillae

2.11.3 Otorhinolaryngology

Iontophoresis is a preferred method for obtaining anaesthesia of the tympanic membrane prior to simple surgical procedures involving that structure. Iontophoresis of zinc has also been used for the treatment of patients with allergic rhinitis.

2.11.4 Ophthalmology

Iontophoresis has been used experimentally to deliver antibiotics into the eye. The principal disadvantage of this technique is the time required for direct contact of the electrode with the eye.

2.11.5 Diagnostic Applications

Iontophoretic application of the drug pilocarpine produces intense sweating, allowing sufficient amounts of sweat to be collected and analyzed. This is now accepted as the primary test in the diagnosis of cystic fibrosis.

3. Conclusion

Transdermal drug delivery system (TDDS) established itself as an integral part of novel drug delivery systems. Transdermal patches are polymeric formulations which when applied to skin deliver the drug at a predetermined rate across dermis to achieve systemic effects. Transdermal dosage forms, though a costly alternative to conventional formulations, are becoming popular because of their unique advantages. Controlled absorption, more uniform plasma levels, improved bioavailability, reduced side effects, painless and simple application and flexibility of terminating drug administration by simply removing the patch from the skin are some of the potential advantages of transdermal drug delivery. Development of controlled release transdermal dosage form is a complex process involving extensive efforts.

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