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Review Article

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Expanding opportunities for transdermal delivery systems: An overview

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ABSTRACT

The most superficial and least permeable skin layer, the stratum corneum, both from structural and compositional viewpoint, provides a uniquely impressive resistance to molecular transport both from and into the body. Studies have been carried out to find safe and suitable permeation enhancers to promote the percutaneous absorption of a number of drugs. The permeation of drug through skin can be enhanced by both chemical penetration enhancement and physical methods. In this review, we will discuss novel aspects of transdermal technology (chemical enhancers, iontophoresis, and ultrasound-enhanced delivery) with their probable mechanisms of action represent new avenues of considerable potential and challenge

Key words: Skin, Permeable,Transdermal,Percutaneous,Penetration enhancement.

INTRODUCTION

More radical approach has been to explore newer interfaces on the body for introducing therapeutics. One such approach, transdermal drug delivery, makes use of human skin as a port of entry for systemic delivery of drug molecules [1]. Transdermal Drug Delivery Systems (TDS) platforms may represent one of the opportunities that can help the industry remain successful in meeting the needs of patients as well as obligations to investors [2].

The first transdermal patch was approved in 1981 for the relief of the symptoms of motion sickness, nausea, and vomiting. There are now more than 35 transdermal products, containing at least 13 approved molecules [3]. New technology, in the form of adjuvants that boost the transfer across the skin barrier, as well as 'active' delivery that uses some form of energy to convey the ingredient, are poised to accelerate this growth[4].Transdermal drug delivery offers the following advantages over the oral route [5, 6,7]

- Facilitates sustained delivery of drug, achieving a steady-state profile. This reduces the likelihood of peak-associated side effects, and ensures that drug levels are above the minimal therapeutic concentration.
- Reduced dosing frequency – (e.g., fentanyl patch provides 72 hour pain relief).
- Avoids 1st pass metabolism.
- Avoids variables that affect drug absorption in the gastrointestinal tract, such as pH, enzymatic activity and drug-food interactions.
- Convenient, non-invasive means of drug delivery.
- Ease of use negates the need for specialized healthcare staff to administer drugs, potentially reducing treatments costs.
- Dosage form can be easily removed in the event of toxicity.
- Provides an alternative route when the patient is unable to take drugs orally, e.g., nauseated and unconscious.

The biggest challenge in transdermal drug delivery today is to open the skin safely and reversibly to these high molecular weight hydrophilic drugs. Several technological advances, physical and chemical methods have been made in the past couple of decades to overcome this challenge. Physical methods employed for increasing transport of drug molecules across the skin use some form of mechanical, electrical, magnetic or thermal energy source to promote transport of macromolecules by disrupting the skin membrane. Chemical permeation enhancers are relatively inexpensive and easy to formulate, they offer flexibility in their design, are simple in application and allow the freedom of self administration to the patient[8]. The release of therapeutic agent from a transdermal formulation applied to the skin surface by (a) dissolution within the release from the formulation, (b) partitioning into the skin's outermost layer, the stratum corneum (SC), (c) diffusion through the SC, principally via a lipidic intercellular pathway, (i.e., the rate- limiting step for the most compounds), (d) partitioning from the SC into the aqueous viable epidermis, (e) diffusion through the viable epidermis and into the upper dermis, and (f) uptake into the local capillary network and eventually the systemic circulation [9,10].

Drug molecules in contact with the skin surface can penetrate by three potential pathways: through the sweat ducts, *via* the hair follicles and sebaceous glands (collectively called the shunt or appendageal route), or directly across the stratum corneum (Fig. 1). The majority of skin penetration enhancement techniques being focused on increasing transport across the stratum corneum rather than via the appendages [11,12].

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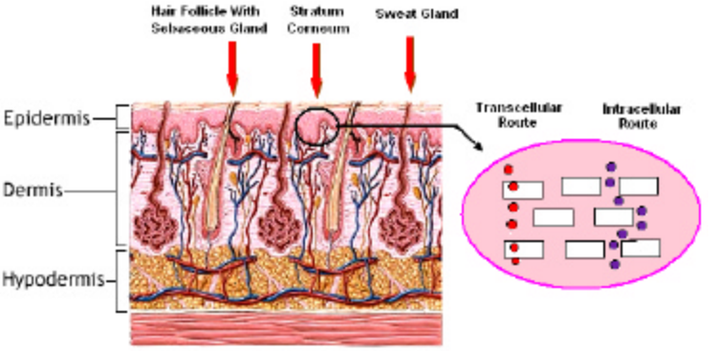

Fig.1. Drug penentration pathway through skin[13]

Moreover, the rate at which permeation occurs is largely dependent on the physicochemical characteristics of the penetrant, the concentration of permeant applied, the partition coefficient of the permeant between the SC and the vehicle as well as the diffusivity of the compound within the stratum corneum[14]. Drug diffusion across the stratum corneum obeys Fick's first law (equation 1), where steady-state flux (J) is related to the diffusion coefficient (D) of the drug in the stratum corneum over a diffusional path length or membrane thickness (h), the partition coefficient (P) between the SC and the vehicle and the applied drug concentration (C_0) which is assumed to be constant[15]:

$$\frac{dm}{dt} = J = DC_0\frac{P}{h}$$

MAXIMIZING TRANSDERMAL DRUG THERAPY

The majority of skin penetration enhancement techniques being focused on increasing transport across the stratum corneum[16]. An overview of techniques to optimise drug permeation across skin is given is given in Figure 1. The stratum corneum consists of 10-15 layers of corneocytes and varies in thickness from approximately 10-15 µm in the dry state to 40 µm when hydrated [17,18]. It comprises a multi-layered "brick and mortar" like structure of keratin-rich corneocytes (bricks) in an intercellular matrix (mortar) composed primarily of long chain ceramides, free fatty acids, triglycerides, cholesterol, cholesterol sulfate and sterol/wax esters[19]. In the initial layers of the stratum corneum this extruded material rearranges to form broad intercellular lipid lamellae, which then associate into lipid bilayers [20,21] with the hydrocarbon chains aligned and polar head groups dissolved in an aqueous layer (Figure. 2). The hydrocarbon chains are arranged into regions of crystalline, lamellar gel and lamellar liquid crystal phases thereby creating various domains within the lipid bilayers[22]. Water is an essential component of the stratum corneum, which acts as a plasticizer to prevent cracking of the stratum corneum and is also involved in the generation of natural moisturizing factor (NMF), which helps to maintain suppleness[23].

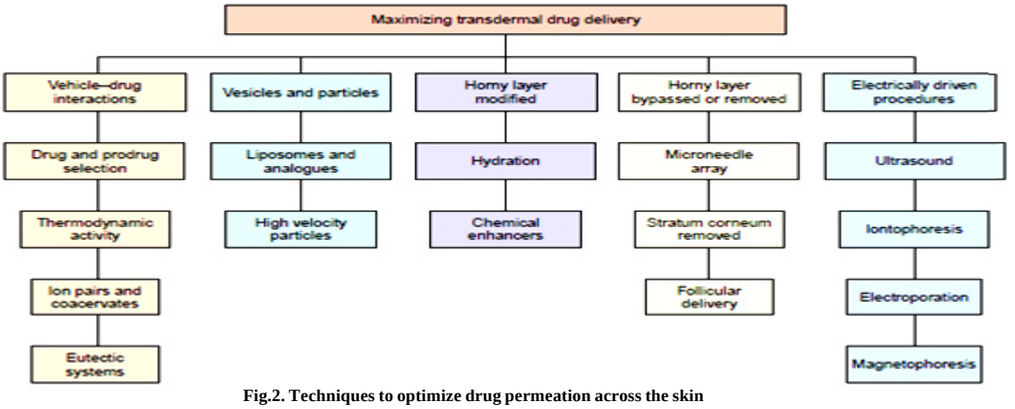

Fig.2. Techniques to optimize drug permeation across the skin