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Review

Electrical, magnetic, photomechanical and cavitational waves to overcome skin barrier for transdermal drug delivery

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ABSTRACT

Transdermal drug delivery is hindered by the barrier property of the stratum corneum. It limits the route to transport of drugs with a log octanol–water partition coefficient of 1 to 3, molecular weight of less than 500 Da and melting point of less than 200 °C. Active methods such as iontophoresis, electroporation, sonophoresis, magnetophoresis and laser techniques have been investigated for the past decades on their ability, mechanisms and limitations in modifying the skin microenvironment to promote drug diffusion and partition. Microwave, an electromagnetic wave characterized by frequencies range between 300 MHz and 300 GHz, has recently been reported as the potential skin permeation enhancer. Microwave has received a widespread application in food, engineering and medical sectors. Its potential use to facilitate transdermal drug transport is still in its infancy stage of evaluation. This review provides an overview and update on active methods utilizing electrical, magnetic, photomechanical and cavitational waves to overcome the skin barrier for transdermal drug administration with insights into mechanisms and future perspectives of the latest microwave technique described.

Contents

1. Introduction

Skin comprises approximately 15% of the total adult body weight and has a surface area about 2 m^2 [1]. The stratum corneum is the outermost layer of skin and the principal barrier to molecular transport across the skin and into the systemic circulation (Fig. 1) [2]. The stratum corneum consists of 10 to 15 layers of anucleated corneocytes (polygonal, elongated and flat; 0.2 to 1.5 μm thick; 34 to 46 μm wide) with thickness varying between 10 and 15 μm in dry state and 40 μm in hydration state [2,3]. These corneocytes are filled with a matrix of crosslinked keratin fibers which are negatively charged at physiological conditions and responsible for the mechanical build up of the stratum corneum [4]. The keratin-rich corneocytes are arranged in brick-and-

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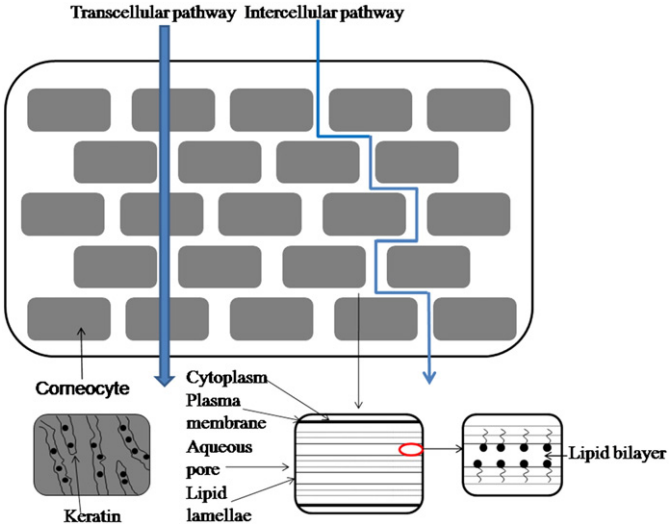

Fig. 1. Schematic diagrams of stratum corneum anatomy and transdermal drug delivery pathways.

mortar like structure with intercellular matrix made of long chain ceramides, free fatty acids, triglycerides, cholesterol, cholesterol sulfate and sterol/wax esters, and intercellular spaces occupying 5 to 20% of the volume of stratum corneum [2,3,5]. The lipid lamellae are associated into lipid bilayer with hydrocarbon chains arranged in crystalline, lamellar gel and lamellar liquid crystal phases, and polar head groups into aqueous phase. The pH of skin surface is about 5 [4]. With pKa values of approximately 8, the head groups of stratum corneum lipids only ionize to a small extent. The physiological pH rises to 7.4 in deeper layers of stratum corneum. A greater population of lipids in this region is ionized with fatty acids of pKa between 4.8 and 6.3 responsible for negative net charge of skin.

Beneath the stratum corneum and epidermal layers is the dermis [1]. The dermis is thicker (approximately 1 to 4 mm) than the epidermis. The main extracellular matrix components of the dermis are collagen and elastin fibers. In the dermis, both blood capillaries and nerve endings are embedded [6].

2. Transdermal drug delivery

Trandermal drug delivery is mediated through direct transfer across the stratum corneum, through the sweat glands, or via hair follicles and sebaceous glands (shunt or appendageal route) [3]. It is recognized that appendages occupy an area for surface permeation of approximately 0.1% [3]. Their contribution to transdermal drug permeation can be minimal except in iontophoresis whereby electrical charges are used to drive the drug molecules into the skin via shunt routes as they provide less electrical resistance [3,7]. The transdermal drug permeation via stratum corneum can be mediated via transcellular (intracellular) or intercellular route (Fig. 1) [1,3]. Using transcellular route, a drug molecule will need to partition and diffuse through keratinocytes after keratinocytes with 4 to 20 lipid lamellae between adjacent keratinocytes. That being so, the intercellular route is deemed to be a more feasible route of delivery. Ideally, the transdermal drug diffusion is promoted when the molecules are characterized by a log octanol-water partition coefficient of 1 to 3, molecular weight of less than 500 Da and melting point of less than 200 °C [1,3,7]. Using intercellular route, the diffusion of hydrophilic drug molecules is limited by the lipid environment of stratum corneum [5]. The hydrophobic drug molecules can partition into the intercellular lipids of stratum corneum. However, its partition into epidermis is restricted by the surrounding aqueous pores.

The transdermal drug delivery can be quantified by flux of what is expressed as the cumulative amount of drug permeates through a specified area of skin over a time interval as follows [8–10]:

$$J = V(dc/dt)/A = PC_o \tag{1}$$

or

$$J = KD_mC_o/h \tag{2}$$

where J = steady state flux, V = receptor fluid/blood volume, dc/dt = change of drug concentration, c with time, t, A = effective diffusional skin area, C_o = drug concentration in donor compartment/dosage form, P = permeability coefficient of drug, K = partition coefficient of drug, D_m = diffusion coefficient of drug and h = skin thickness. The enhancement extent of transdermal drug flux by dosage form and/or other external stimuli can be expressed by enhancement ratio (ER) as follows:

$$\text{ER} = \text{Flux of drug in presence of external stimuli}/\text{Flux of drug in absence of external stimuli.} \tag{3}$$

Transdermal drug delivery offers several advantages over oral and injection routes of administration [11]. Its application is convenient, painless, non-invasive and allows rapid termination of therapy when adverse effects develop. Transdermal drug administration avoids pre-systemic and systemic first pass metabolism [11,12]. It can provide controlled drug release over extended periods of time. However, the daily dose of a drug that can be delivered across the skin ranges between 5 and 10 mg [3]. Over the past years, extensive efforts have been devoted to design transdermal delivery technology with the aim to circumvent the limitation in administration to potent drugs only.

The transdermal drug delivery technology can be broadly classified into two categories: passive and active methods with the latter requiring an external source of energy to enhance skin permeability to drugs [1,13]. Passive methods, on the other hand, utilize chemical permeation enhancers, biological peptides or formulation approaches. The execution of passive methods is relatively straightforward. Nevertheless, these methods give rise to a lag time up to hours and cannot be adopted when rapid drug action or irregular administration schedule is concerned [13–15]. The active methods have gained a widespread attention by academic and industrial researchers [13]. Active devices have been commercialized and subjected to clinical assessment. These techniques increase the transdermal drug transport through physical disruption of the skin barrier. They induce transient permeabilization of stratum corneum to enable delivery of hydrophilic and macromolecular drugs with reduced lag time, and adjustable treatment and device parameters taking into consideration the skin properties of the individual.