

# Performance of transdermal therapeutic systems: Effects of biological factors

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## Abstract

Transdermal drug delivery (TDD) is a technique that is used to deliver a drug into the systemic circulation across the skin. This mechanism of drug delivery route has many advantages, including steady drug plasma concentrations, improved patient compliance, elimination of hepatic first pass, and degradation in the gastrointestinal tract. Over the last 30 years, many transdermal products have been launched in the market. Despite the inherent advantages of TDD and the growing list of transdermal products, one of the major drawbacks to TDD is the occurrence of inter- and intraindividual variation in the absorption of the drug across the skin. A majority of these variations are caused by biological factors, such as gender, age, ethnicity, and skin hydration and metabolism. These factors affect the integrity and the barrier qualities of the skin, which subsequently result in the variation in the amount of drug absorbed. The main objective of this review article is to provide a concise commentary on the biological factors that contribute to the variation in transdermal permeation of drugs across human skin and the available transdermal therapeutic systems that may reduce the variations caused by biological factors.

**Key words:** Percutaneous permeation, therapeutics system, variation in skin absorption

## INTRODUCTION

The application of medicinal substances onto the skin has been practiced since ancient times in order to cure a variety of ailments, including severe chest congestion—by applying a mustard plaster. Today, transdermal drug delivery (TDD) utilizes the skin as a portal to deliver drugs into the systemic circulation. The development of the first transdermal therapeutic system or “patch” containing scopolamine for motion sickness in the early 1980s heralded the start of this route becoming a viable treatment option.<sup>[1]</sup> Now several transdermal products are being marketed successfully incorporating drugs, such as clonidine, nicotine, scopolamine, nitroglycerin, estradiol, and fentanyl.<sup>[2]</sup> The market value for the transdermal products is

believed to be worth approximately \$3 billion annually in the USA alone.<sup>[3]</sup> One of the disadvantages of the transdermal route is the variations in inter- and intraindividual absorption of drugs applied to the skin.<sup>[4]</sup> These variations are a result of biological factors that exist between and within individuals.<sup>[5]</sup> This review briefly covers the subject of human skin anatomy and the type of transdermal therapeutic systems (TTS) that are currently available, which facilitate a better understanding of the core topic of this article. Biological factors, such as gender, age, ethnicity, disease, skin hydration, and application site, all of which may cause variability in drug absorption across the skin, are discussed as are the transdermal delivery systems, which may be employed to overcome these variations.

## ANATOMY OF HUMAN SKIN

The skin is the largest organ in the body, and it accounts for approximately 10% of an individual’s body mass. Its large surface area means that the skin is a feasible portal for delivering potent drugs for systemic effect. The skin can be broken down into 3 layers, namely, the epidermis, dermis, and hypodermis, with each layer being physically and functionally distinct.<sup>[6]</sup> The inferior layer is the hypodermis, which is largely made up of adipose tissue and mainly functions as an insulator, cushion, and also as a storehouse of high energy reserve in the form of the triglycerides present. Above this layer is the dermis, which is about 2–3 mm thick and consists of connective tissues, which adhere to the epidermis and the hypodermis. The dermis is where numerous

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structures, such as pilosebaceous units, blood vessels, lymphatic vessels, nerve endings (sensory receptors), and sweat glands are located. The epidermis is made up of stratified squamous epithelial tissue, which can be classified into 5 different layers based on keratinocyte proliferation and differentiation. These layers, starting with the outermost, are the *stratum corneum* (SC), *stratum lucidum* (SL), *stratum granulosum* (SG), *stratum spinosum*, and *stratum basale* (SB). The SC is the final product of the epidermal cell differentiation process and the overall SC structure forms a natural barrier, which prevents excessive water loss and the ingress of exogenous chemicals, including drugs, which limits the use of the transdermal route as a means of systemic drug delivery.<sup>[7]</sup> It is composed of 10–15 rows of cells and is 10  $\mu\text{m}$  thick. It consists of anucleated and highly keratinized cells, known as corneocytes or keratinocytes, embedded in a lipid matrix. The SC undergoes a total turnover, every 2–3 weeks.<sup>[8]</sup> SC keratinocytes are surrounded by a continuous lipid phase known as the intercellular lipid lamellae, and has been said to resemble a “bricks and mortar” model.<sup>[9]</sup> The major components in the SC lipid lamellae include 8 different classes of ceramides, fatty acids, cholesterol sulfate, and cholesterol. The lipid lamellae structure was further studied by Forslind and a domain mosaic model was proposed.<sup>[10]</sup> His work showed that the lipids were differentiated into a crystalline lipid region, which allows the SC to function as a barricade, and this is bordered by a more fluid lipid region, that facilitates the uptake of water allowing the keratinocytes to remain hydrated. The ability to remain hydrated helps to prevent the formation of fissures at the skin surface.

## TRANSDERMAL THERAPEUTIC SYSTEMS

The transdermal route promises a safe, reproducible method of drug delivery, with optimal patient compliance. However, the usefulness of this route is limited by the fact that the SC forms such an excellent barrier to exogenous chemicals.<sup>[11]</sup> The successful delivery of a drug across the skin depends on the physicochemical properties of the drug, such as molecular weight (<500 Da), partition coefficient (1–3) and the potency of the drug, which is recommended to be below 20 mg IV dose/day.<sup>[12]</sup> However, when dealing with a drug that falls outside of these ranges, the key to successful TDD relies on a high-performance drug delivery device.<sup>[13]</sup> An efficient TTS must be capable of temporarily reducing or bypassing the SC barrier with the result of enhanced drug delivery to attain a therapeutic plasma drug concentration. Transdermal dosage forms include ointments, creams, gels, and, more commonly, the transdermal “patch.” More recently, newer dosage forms have been launched, such as the metered dose aerosols and ballistic needleless injections.<sup>[14–16]</sup> The transdermal patch is often favored because the other semi-solid formulations rely on the patient applying the correct amount of the formulation to their skin as the main method of graduating the dose.<sup>[17]</sup> The concentration of drug in the dosage form and the area of skin to which it is applied are important parameters that affect the permeation rate. This is difficult to achieve using semi-solid dosage forms.<sup>[18]</sup> Depending on the type

of transdermal patch used, the formulation may consist of some or all of the following components: drug, release liner, adhesive, rate-limiting membrane, backing layer, and other excipients. The release liner is used to seal the area of the formulation that will be directly applied to the patient’s skin. The presence of a release liner is necessary to control any unintentional release of drug during transport or storage and also to prevent the formulation adhering to the packaging. The backing layer (the area of the formulation that is visible after application) forms a protective covering before and during use and it may also have the effect of occluding the skin and therefore raising the hydration level of SC, which may aid drug permeation across the skin. The rate-limiting membrane is used to prevent leakage from a semi-solid or liquid reservoir while also ensuring that the release of the drug from the reservoir occurs at the desired rate. The adhesive keeps the patch firmly attached to the skin surface for the duration of use, which may be up to 7 days. In general, transdermal patches may be classified into 3 groups, which are the matrix patch, reservoir patch, and drug-in-adhesive patch.<sup>[19]</sup> Drug-in-adhesive formulations contain the drug directly incorporated in the adhesive layer, while in the matrix patch the drug is contained in a polymer matrix, which controls the release of the drug. The reservoir patch contains the drug in a liquid reservoir behind a leak-proof rate-limiting membrane. The drug-in-adhesive patch is normally used for when a drug is capable of readily permeating the skin. Examples of such include formulations containing lidocaine (Lidoderm<sup>®</sup>), nitroglycerine (Deponit<sup>®</sup> and Minitran<sup>®</sup>), and nicotine (Nicotrol<sup>®</sup> and Habitraol<sup>®</sup>). Matrix and reservoir formulations are often used when the drug is incompatible with, or insufficiently soluble in the transdermal adhesive. However, the optimal design of a TTS in itself may not necessarily provide a therapeutic drug plasma concentration. Chemical or physical enhancement techniques may be necessary to overcome the SC, and in the last few decades numerous methods have been investigated.<sup>[20]</sup> However, only a handful of these techniques have demonstrated significant improvements in transdermal flux. Among these are supersaturated drug solutions, melting point depression, microfabricated needles, and inclusion of potent safe chemical permeation enhancers. The increasing numbers of patents being applied for and granted for newer techniques suggests the likelihood of more effective TTS in the near future.<sup>[21]</sup>

## GENDER-BASED VARIATION

One of the differences between male and female skin is keratinocyte size, with those cells found in male skin samples tending to be somewhat larger than those present in skin from female donors. The length of keratinocytes present in skin from male donors is reported to range from 37 to 46  $\mu\text{m}$ , whereas keratinocytes found in skin from female donors typically ranges from 34 to 44  $\mu\text{m}$ .<sup>[22]</sup> Other differences between male and female skin is that men tend to have larger skin pores sizes (sweat and sebaceous gland) and they also have more active sebaceous glands compared with those in female skin.<sup>[23]</sup> The pH of male skin is also significantly lower than the female skin.<sup>[24]</sup> These differences

could potentially translate into variation in transdermal drug permeation, however, most studies have demonstrated that there is no difference in the permeability of male and female skin. Transepidermal water loss (TEWL), which is often used as a measure of skin barrier integrity, has been shown to be the same in both sexes.<sup>[25]</sup> Similarly, another study showed that there was no significant difference between the permeation of nicotine across female and male skin under *in vivo* conditions.<sup>[26]</sup> However, because data is scant, no generalizations about gender-based variations in transdermal delivery can be firmly drawn. Experiments that employ a range of drugs with differing polarities should be used to judge whether there are indeed real differences in the permeation of drugs across male and female skin.

## AGE-BASED VARIATION

The relationship between age and skin structure has been extensively studied since the mid-1980s.<sup>[27]</sup> There is a clear evidence of skin structural changes, while the aging process takes place, such as the thinning of the epidermis and dermis, the loss of adherence between the keratinocytes, a decrease in the number of melanocytes and Langerhans cells, and an increase in type 3 collagen fibers.<sup>[28]</sup> The important question here should be, whether or not the skin structural changes have any effect on transdermal absorption. It is an important issue because transdermal formulations are designed to be applied to the skin of patients of all ages. The literature enlightens 2 different opinions. The first suggests that the SC remains intact and invariable during the course of a human life in spite of the other general changes that occur.<sup>[22]</sup> Conversely, some researchers have demonstrated that the permeation of the nonlipophilic compounds: hydrocortisone, benzoic acid, acetylsalicylic acid, and caffeine were significantly lower in the elderly compared with young subjects.<sup>[27]</sup> However, in the same study, it was found that the absorption of testosterone and estradiol was similar between both the elderly and the younger subjects, implying that the permeation of hydrophobic drugs remains unaffected by age but the permeation of less lipophilic compounds does depreciate with age. This study suggests that aging can affect the permeation of hydrophilic compounds across the skin. It is speculated that this is related to the lower water content of the SC that is evident with the decreasing natural moisturizing factor (NMF).<sup>[22]</sup> Consequently, the lower water level in the SC leads to the loss of a polar route across the SC lipid lamellae, which then obstructs the movement of hydrophilic compounds across the skin. Although an occlusive patch may increase the water content of the SC, the total retention might still be inferior to skin that contains a high level of NMF. Thus, a TTS that delivers a drug directly into the lower epidermis, such as a formulation containing microfabricated needles, may reduce age-based variations in drug delivery because the SC is not the limiting factor. Similarly, the permeation of drug (theophylline and caffeine) across neonatal skin has been shown to be superior compared with healthy adult skin.<sup>[29,30]</sup> This is because the skin takes 3–5 months after birth to mature and attain a similar thickness and barrier capabilities

as those of an adult.<sup>[22]</sup> This delay in maturation is because cell and tissue differentiation that occurs in the epidermis has not been completed.<sup>[31]</sup> One of the key aspects of skin maturation is the formation of intercellular lipid regions within the SL and SC layers. These lipids are synthesized *in situ* in the SB, SP, and SG, where they can be viewed as lamellar bodies (LB). The lipids present in these LB include sphingomyelins, glucosylceramides, phospholipids, and cholesterol, however, the lipids found in the intercellular regions of the SC comprise largely of cholesterol-sulfate, free fatty acids and, notably, ceramides. This change in SC composition is a key requirement to the integrity of the barrier that requires extracellular processing to take place, such as the conversion of glucosylceramides to ceramides by the enzyme  $\beta$ -glucocerebrosidase; conversion of sphingomyelins by acid sphingomyelinase to ceramides (type 2 and 5), and the phospholipids are degraded by phospholipase A<sub>2</sub> enzyme to give free fatty acids.<sup>[32,33]</sup> Until the mature skin barrier forms, the permeability of neonatal skin is high, increasing the possibility of successful transdermal therapy. Therefore, in theory, it should be possible to deliver a greater number of drugs via the transdermal route to neonates than would be possible in adults. However, because neonates requiring systemic drug therapy are often, by definition, in a critical condition, it is likely that drugs would be administered parenterally.

## ETHNICITY-BASED VARIATION

Transdermal formulations are designed for the general population regardless of skin type or ethnicity.<sup>[5]</sup> But, importantly, a number of studies that have documented variations in percutaneous absorption based on ethnicity. One of the earliest studies that highlighted this demonstrated that the permeation of fluocinolone acetonide was higher across Caucasian skin compared with Afro-Caribbean skin.<sup>[34]</sup> Typically, studies of this nature have tended to compare Caucasian and Afro-Caribbean skin, and it was noted that permeation across Afro-Caribbean skin was often lower.<sup>[25,35-37]</sup> These differences in permeation are purported to be due to the notable differences in skin structure observed between different races. Afro-Caribbean skin has a greater number of keratinocyte layers within the SC, thus suggesting that the density of the SC is greater.<sup>[37]</sup> The integrity of the SC is thought to be further amplified in Afro-Caribbean skin by the high cellular cohesion between keratinocytes and the higher lipid content in the SC.<sup>[38]</sup> Other studies have shown that there are differences in the water content of the SC, with skin from Afro-Caribbean subjects having a lower SC water content compared with other races.<sup>[39,40]</sup> A separate study compared the variation in skin permeation of methyl nicotinate as a model drug between 4 different ethnic groups. It was found that the rank order of skin permeability was Afro-Caribbean < Asians < Caucasians < Hispanics.<sup>[41]</sup> Based on this observation, clinicians should be aware that plasma drug levels obtained following TDD may not be as high in Afro-Caribbean patients when compared with Caucasian patients. Moreover, the TSS used should, if possible, be able to reduce these differences leading to relatively

consistent drug plasma concentration for at least the majority of individuals. The use of microfabricated needles, thus avoiding the SC barrier, may be useful in this aim.

## SKIN HYDRATION

Skin hydration is another biological factor that affects the percutaneous permeation of many drugs across the skin. Water only accounts for about 10%–20% of the weight of the stratum corneum at normal physiologic conditions; however, if the skin is soaked in water for a short period of time, the SC can absorb up to 20 fold more water than would normally be present.<sup>[42]</sup> The hydration level of the SC often varies due to certain disease states, such as eczema and ichthyoses and also the ambient humidity and temperature. NMF is known to act as a mediator for the hygroscopic property of the stratum corneum.<sup>[22]</sup> NMF consists of free amino acids and amino acid salts, which are derived from the hydrolysis of proteins, such as fillagrin. Some researchers have suggested that hydration of the skin causes swelling of the keratinocytes which, in turn, affects the SC lipid packing. These disruptions can lead to a merging of the interrupted polar and nonpolar intercellular routes to form a continuous polar and nonpolar route across the SC, which can increase the flux of some permeants.<sup>[43]</sup> However, the study by Van Hal *et al* found that there was no major modification in the lipid packing except for the presence of discrete water pools in the SC lipids.<sup>[44]</sup> It seems that at the present time there is no conclusive evidence for the mechanism of permeation enhancement caused by SC hydration. Formulation scientists have tried to take advantage of the increase in permeation caused by skin hydration by including nonporous linings on transdermal formulations to deliberately occlude the skin surface so that the hydration of the SC is increased. However, this approach has its drawbacks in that interindividual variations in SC hydration may lead to variable drug absorption, irritation, and subpatch microbial growth. The intensity of irritation varies based on individual skin sensitivity.<sup>[45]</sup>

## SKIN TEMPERATURE

Distinct from the internal body temperature, which is maintained at around 37°C, the skin temperature is influenced by environmental factors, such as ambient temperature, circulation of air, and humidity, which can cause the temperature of the skin to vary considerably. Cautions on the avoidance of exposure of the TTS to extreme sunlight or heat have often been included in the patient information leaflet, one such example is the Lidoderm<sup>®</sup>, which is a local analgesic preparation. This difference in skin temperature could lead to the increased or decreased drugs flux across the skin. The permeability of the skin is directly proportional to its temperature, with higher temperatures causing increased fluidization of the SC lipid domain, leading to an increase in the diffusion coefficient of the drug.<sup>[46]</sup> More interestingly, the skin surface temperature has been shown to vary with an individual's emotional/psychological state as the result of the sympathetic/parasympathetic nervous system.<sup>[47]</sup>

An occlusive/insulating dressing, which could reduce the loss of heat from the skin, is likely to reduce the fluctuations in skin temperature at the site of application.<sup>[48]</sup> Although this simple approach is a suitable method for maintaining a more constant skin temperature, it may cause a slight elevation in the local temperature.<sup>[49]</sup>

## DISEASE STATE

The skin comes into direct contact with the environment and hence it is often the first part of the body that sustains damage if an individual is exposed to an irritant substance. Damaged or diseased skin has been shown to be considerably more permeable compared with intact skin.<sup>[17]</sup> Ichthyoses, dermatitis, impetigo, eczema, and psoriasis are all fairly common skin diseases that can result in a reduction in the barrier nature of the skin. Inflammation occurs as a response to mechanical, chemical, thermal, and microbial assault. Radiation in the form of UV light can also initiate the inflammatory process. The inflammatory response can result in a reduction in the barrier properties of the SC, which can lead to the increased skin permeability to drugs. It has been shown that the *in vivo* permeation of hydrocortisone across normal healthy human skin is lower than it is across skin containing psoriatic lesions.<sup>[50]</sup> TDD is best avoided when the skin is diseased, as barrier defects caused by certain conditions could lead to overabsorption of drugs, leading to adverse drug reactions.

## SKIN METABOLISM

The skin is a metabolically active organ and passage across the skin will expose the drug to a variety of enzymes located in the skin. Enzymes involved in Phase I (oxidation, reduction, and hydrolysis) and Phase II (methylation, glucuronidation) metabolic processes have all been isolated from the skin. A majority of these enzymes have been detected in the epidermis and the appendages of the skin and interestingly enzyme activity has also been detected in the SC.<sup>[51]</sup> Collectively, these enzymes contribute to first-pass skin metabolism, which can decrease the bioavailability of the compound applied to the skin surface. Furthermore, a drug applied to the skin can also be metabolized by some microbes, such as *Staphylococcus epidermidis*, which may be present on the skin surface and within the superficial layers. In spite of the variety of enzymes present, the total enzymatic activity of skin is far lower than that of the liver. Skin first-pass metabolism is estimated to be only 10% of that which takes place in the liver.<sup>[52]</sup> Thus, depending on the amount of enzymes that are present and the nature of the drug (tertiary esters are far more stable than primary esters to skin hydrolysis), the degree of metabolism that takes place may vary considerably.

## ANATOMICAL SITE VARIATION

Skin structure does not only vary among individuals, it also varies between different anatomical sites within an individual. For

example, the epidermis is up to 13 times thicker at the weight-bearing soles of the feet and the palms of the hand compared with that of the eyelids or the lips. It is often regarded that the SC thickness is directly related to drug permeability resistance, where one would have thought that drug permeation across the soles or palms would be lower compared with that across the skin of the eyelid or lips. Interestingly, this is not always the case, as similar permeation profiles have been achieved between regions with different SC thickness, and different drug permeation profiles were achieved between sites with similar SC thickness.<sup>[50]</sup> However, other studies have shown that the permeability of the skin varies between different anatomical sites around the body, for example, the permeation of testosterone across the scrotal skin was 5 times greater than the permeation rates at other anatomical sites.<sup>[4,7]</sup> Skin from other sites, however, such as the arm and chest, show very similar barrier properties: clonidine application was shown to result in very similar plasma concentrations.<sup>[4]</sup> Consequently, a hierarchy of permeability at different anatomical sites can be generalized, where the skin at the epigenital region is said to have the highest permeability followed by skin from the head and neck region, the skin at the trunk (chest, stomach, back), the skin at the arm, and finally the skin of the legs.<sup>[22]</sup> The main factors that influence the choice of application site are the consideration of the adhesiveness of the patch to the skin: ease of removal and mitigation of the irritation potential is of importance. As such, it is often recommended that transdermal formulations should be applied to the trunk or the arm as there is usually less potential for sensitization and the lower density of hair follicles leads to better tack and ease of removal. This is also because the skin of the trunk or the arm creases less during physical activity. Some examples of transdermal patches on the market that are applied to the skin of the trunk or the arm are Duragesic<sup>®</sup> (fentanyl), Androderm<sup>®</sup> (testosterone), Nitrodisc<sup>®</sup> (Nitroglycerine), Habitrol<sup>®</sup> (nicotine), Catapres-TTS<sup>®</sup> (clonidine), and Nicotrol<sup>®</sup> (nicotine). However, some manufacturers recommend different sites of the application, such as the Lidoderm<sup>®</sup> (lidocaine) TTS, which is recommended to be applied at the site where pain is felt. Furthermore, it is suggested that Transderm Scop<sup>®</sup> (scopolamine) is applied at the back of the ear; Climara and Vivelle (both containing estradiol) should be applied to the lower abdomen or the upper part of the buttocks. The variation in the application site is mainly attributed to the type of drug and the permeability across the skin. For example fentanyl, nitroglycerine, clonidine, and nicotine have a relatively high permeability due to the optimal log P (1–3) and low molecular mass (<500), thus the site of application has minimal effect on the permeation of these drugs.<sup>[12]</sup> It is recommended that formulations containing drugs, such as lidocaine and scopolamine be applied at specific regions in order to increase the desired effect. Lidocaine applied at the site of pain may lower the perceived pain more rapidly because the amount of drug being delivered to the affected area is higher. However, it should be borne in mind that for the ease of application and removal, the application of patches at any hairy region should be avoided if possible, or otherwise hair removal before application may be necessary.

## CONCLUSION

The biological variation described in this review could well translate into significant variation in drug delivery via the transdermal route. As a consequence, preventive steps must be taken to avoid perilous generalizations when prescribing transdermal products. Specific instructions should always be included on the patient information leaflet and the summary of product characteristics, such as defining the area of application and exact duration of application. Furthermore, the recommended dosage instructions should take into account different patient groups based on ethnicity, age, and gender. Factors, such as skin temperature and skin hydration level, should be controllable by the transdermal dosage form in order to reduce variation in drug absorption.

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## REFERENCES

1. Hadgraft J, Lane ME. Skin permeation: The years of enlightenment. *Int J Pharm* 2005;305:2-12.
2. Honeywell-Nguyen PL, Bouwstra JA. Vesicles as a tool for transdermal and dermal delivery. *Drugs Today* 2005;2:67-74.
3. Langer R. Transdermal drug delivery: Past progress, current status, and future prospects. *Adv Drug Deliv Rev* 2004; 56:557-8.
4. Farahmand S, Maibach HI. Transdermal drug pharmacokinetics in man: Interindividual variability and partial prediction. *Int J Pharm* 2009;367:1-15.
5. Kumar R, Philip A. Modified transdermal technologies: Breaking the barriers of drug permeation via the Skin. *Trop J Pharm Res* 2007;6:633-44.
6. Walters KA, Roberts MS. The structure and function of the skin. New York: Marcel Dekker; 2002. p. 1-40.
7. Lampe MA, Burlingame AL, Whitney J, Williams ML, Brown BE, Roitman E, *et al.* Human stratum corneum lipids: Characterization and regional variations. *J Lipid Res* 1983;24:120-30.
8. Monteiro-Riviere NA. Comparative anatomy, physiology and biochemistry of mammalian skin. USA: CRC Press; 1991. p. 3-71.
9. Michaels AS, Chandrasekaran SK, Shaw JE. Drug permeation through human skin: Theory and *in vitro* experimental measurement. *Am Ins Chem Eng J* 1975;21:985-96.
10. Forslind B. A domain mosaic model of the skin barrier. *Acta Derma Venereol* 1994;74:1-6.
11. Iman I, Nadia A, Ebtsam MA. Formulation and stability study of chlorpheniramine maleate transdermal patch. *Asian J Pharm* 2010;4:17-23.
12. Hadgraft J. Skin deep. *Eur J Pharm Biopharm* 2004;58:291-9.
13. Garala K, Faldu N, Basu B, Bhalodia R, Mehta K, Joshi B. Chemical penetration enhancement. *J Pharm Res* 2009;2: 1804-8.
14. Magnusson BM, Walters KA, Roberts MS. Veterinary drug delivery: Potential for skin penetration enhancement. *Adv Drug*

- Deliver Rev 2001;50:205-27.
15. Remington JP, Gennaro AR. Remington: The science and practice of pharmacy. Baltimore, Maryland: Lippincott Williams and Wilkins; 2005.
  16. Morgan TM, O'Sullivan HM, Reed BL, Finnin BC. Transdermal delivery of estradiol in postmenopausal women with a novel topical aerosol. *J Pharm Sci* 1998;87:1226-8.
  17. Washington N, Washington C, Wilson CG. Physiological pharmaceuticals: Barriers to drug absorption. London and New York: Taylor and Francis Group; 2001. p. 182-7 .
  18. Mills PC, Cross SE. Transdermal drug delivery: Basic principles for the veterinarian. *Vet J* 2006;172:218-33.
  19. Aggarwal G, Dhawan S. Development, fabrication and evaluation of transdermal drug delivery system: A review. *Latest Rev* 2009. p. 7.
  20. Singh I, Sri P. Percutaneous permeation enhancement in transdermal drug delivery. *Asian J Pharm* 2010;4:92-101.
  21. Shah SH, Shah D. Transdermal drug delivery technology revisited. *Recent Adv Latest Rev* 2008. p. 6.
  22. Williams AC. Transdermal and topical drug delivery: From theory to clinical practice. London: Pharmaceutical Press; 2003.
  23. Giacomoni PU, Mammone T, Teri M. Gender-linked differences in human skin. *J Dermatol Sci* 2009;55:144-9.
  24. Jacobi U, Gautier J, Sterry W, Lademann J. Gender-related differences in the physiology of the stratum corneum. *Dermatology* 2005;211:312-7.
  25. Reed JT, Ghadially R, Elias PM. Skin type, but neither race nor gender, influence epidermal permeability barrier function. *Arch Dermatol* 1995;131:1134-8.
  26. Prather RD, Tu TG, Rolf CN, Gorsline J. Nicotine pharmacokinetics of Nicoderm (nicotine transdermal system) in women and obese men compared with normal-sized men. *J Clin Pharmacol* 1993;33:644-9.
  27. Roskos KV, Maibach HI, Guy RH. The effect of aging on percutaneous absorption in man. *J Pharmacokinetic Pharmacodyn* 1989;17:617-30.
  28. Fore J. A review of skin and the effects of aging on skin structure and function. *Ostomy Wound Manage* 2006;52:24-39.
  29. Evans NJ, Rutter N, Hadgraft J, Parr G. Percutaneous administration of theophylline in the preterm infant. *J Pediatr* 1985;107:307-11.
  30. Amato M, Isenschmid M, Hüppi P. Percutaneous caffeine application in the treatment of neonatal apnoea. *Eur J Pediatr* 1991;150:592-4.
  31. Cartwright RG, Cartlidge PH, Rutter N, Melia CD, Davis SS. Transdermal delivery of theophylline to premature infants using a hydrogel disc system. *Br J Clin Pharm* 1990;29:533-9.
  32. Holleran WM, Takagi Y, Menon GK, Legler G, Feingold KR, Elias PM. Processing of epidermal glucosylceramides is required for optimal mammalian permeability barrier function. *J Clin Invest* 1993;91:1656-64.
  33. Zuo Y, Zhuang DZ, Han R, Isaac G, Tobin JJ, McKee M, *et al.* ABCA12 maintains the epidermal lipid permeability barrier by facilitating formation of ceramide linoleic esters. *J Biol Chem* 2008;283:36624-35.
  34. Stoughton RB. Pharmacology of the skin. New York: Appleton Century Crofts; 1969.
  35. Wedig JH, Maibach HI. Percutaneous penetration of dipyrithione in man: Effect of skin color (race). *J Am Acad Dermatol* 1981;5:433-8.
  36. Berardesca E, Maibach HI. Racial differences in pharmacodynamic response to nicotines *in vivo* in human skin: Black and white. *Acta Dermatol Venereol* 1990;70:63-6.
  37. Weigand DA, Haygood C, Gaylor JR. Cell layers and density of negro and Caucasian stratum corneum. *J Invest Dermatol* 1974;62:563-8.
  38. Rienertson RP, Wheatley VR. Studies on the chemical composition of human epidermal lipids. *J Invest Dermatol* 1959;32:49-59.
  39. Berardesca E, de Rigal J, Leveque JL, Maibach HI. *In vivo* biophysical characterization of skin physiological differences in races. *Dermatologica* 1991;182:89-93.
  40. Singh J, Gross M, Sage B, Davis HT, Maibach HI. Effect of saline iontophoresis on skin barrier function and cutaneous irritation in four ethnic groups. *Food Chem Toxicol* 2000;38:717-26.
  41. Leopold CS, Maibach HI. Effect of lipophilic vehicles on *in vivo* skin penetration of methyl nicotinate in different races. *Int J Pharm* 1996;139:161-7.
  42. Barry BW. Properties that influence percutaneous absorption. New York: Marcel Dekker; 1983. p. 127-233.
  43. Hadgraft J, Guy RH. Transdermal drug delivery: Revised and expanded. 2nd ed. New York: Marcel Dekker; 2006.
  44. Van Hal DA, Jeremiasse E, Junginger HE, Spies F, Bouwstra JA. Structure of fully hydrated human stratum corneum: A freeze fracture electron microscopy study. *J Invest Dermatol* 1996;106:89-95.
  45. Patel S, Maibach HI. Effect of age and sex on elicitation of irritant contact dermatitis. *Contact Dermatitis* 1994;30:257-64.
  46. Roberts MS, Cross SE, Pellet MA. Skin Transport. New York: Markel Dekker; 2002. p. 1-30.
  47. McFarland RA. Relationship of skin temperature changes to the emotions accompanying music. *Appl Psychophys Biof* 1985;10:255-67.
  48. Waterman NG, Stoeckinger J, Goldblatt D. Effects of various dressings on skin and subcutaneous temperatures: A comparison. *AMA Arch Surg* 1967;95:464-71.
  49. Ibrahim T, Ong SM, Saint Clair Taylor GJ. The effects of different dressings on the skin temperature of the knee during cryotherapy. *Knee* 2005;12:21-3.
  50. Wester RC, Maibach HI. Regional variations in percutaneous absorption. New York: Marcel Dekker; 1989. p. 111-20.
  51. Liu P, Higuchi WI, Ghanem AH, Good WR. Transport of beta-estradiol in freshly excised human skin *in vitro*: Diffusion and metabolism in each skin layer. *Pharm Res* 1994;11:1777-84.
  52. Hotchkiss SA. Dermal metabolism. New York: Marcel Dekker; 1998. p. 43-101.

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