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TRANSDERMAL DRUG DELIVERY SYSTEMS INFLUENCING FACTORS, STUDY METHODS AND THERAPEUTIC APPLICATIONS

Ravi Theaj Prakash U and Padma Thiagarajan*

School of Bio Sciences and Technology, VIT University, Vellore-632014, India

***Corresponding author e-mail:** p.padma@vit.ac.in

ABSTRACT

Drug delivery across the skin offers several advantages, which includes bypassing of gastrointestinal tract and deviation from liver metabolism. Several drugs have been successfully assimilated through this route, which is in turn controlled by the drug lipophilicities and molecular weights along with their partition coefficients. The age and condition of the skin are also determining factors. However, an obvious barrier to this process is the stratum corneum which restricts efficient penetration of drugs. This drawback has been partially overcome by the use of permeation enhancers, and also by coercive techniques, which promote easy drug uptake, as proved by various *in vitro* and *in vivo* assays. Consequently, several transdermal delivery based therapeutic systems have been developed to treat various specific pathological conditions. The factors controlling drug uptake and penetration enhancers have been discussed in this review, along with some important therapeutic applications.

Keywords: Transdermal drug delivery, Stratum corneum, Penetration enhancers and Transdermal therapeutics

INTRODUCTION

The transdermal system of drug delivery refers to the route of assimilation of bioactive compounds across the skin. These systems, also known as patches, form one of the most successful routes of drug delivery. Transdermal patches date back to 1980s, when the first of such system, developed by Alza Corporation for treatment of motion sickness, was approved by FDA. [1] Since then, a large number of transdermal drugs have been marketed, which include clonidine for hypertension treatment, estradiol for relief from postmenopausal symptoms, fentanyl for pain management, nicotine to aid in smoking cessation, and nitroglycerin and testosterone for treatment of angina pectoris and hypogonadism respectively. [2] The types and anatomy of these systems and their role in adhesion along with the techniques employed to measure adhesive properties have been reviewed. [3] Drug absorption through the skin may however also have unwanted systemic effects. [4]

This system is advantageous over the oral route of administration, as it bypasses the gastrointestinal tract. Some additional positives include overcoming the first pass liver metabolism, lowered drug plasma levels leading to decreased side effects, reduction in drug dosage concentrations and dosage frequency, low therapeutic index, easy termination of drug assimilation, etc. [5, 6] Despite these positive features, certain problems are posed by topical delivery of drugs, mainly due to the impermeable nature of human skin. The stratum corneum, which acts as a protective layer of the skin is made up of dead cells, filled with keratin fibers and surrounded by the lipid bilayer. [7] It is impermeable to many drugs and allows only a few low molecular weight compounds to pass through it. [8] Therefore, to maximize drug permeability by overcoming this hindrance barrier, transport of drugs through hair follicles has been exploited. [9] Several new formulations have also been prepared for efficient drug penetration which commonly includes ointments, gels powders, creams, etc.

Numerous biological and physicochemical factors influence these systems. The former may be skin conditions, its age and metabolism, and also blood

biochemistry. The latter depends on skin hydration, temperature, and pH and drug concentration. To maximize drug bioavailability, several techniques have been employed, like ionotophoresis and electroporation, etc. The use of sonophoresis, needle arrays and liposomes are also found to be favorable towards this end, as is the degree of skin hydration. This review deals with the factors influencing transdermal drug delivery systems, along with their therapeutic applications. Dermatological vehicles for drug delivery across the skin barrier are also discussed.

STRUCTURE OF HUMAN SKIN AND DRUG PERMEATION

Drugs are known to enter the human body, through various layers of the skin, via intramuscular, subcutaneous and transdermal routes (Figure 1). Skin acts as a major barrier for permeation of any substance into the body and this is mainly due to the stratum corneum, which is its outer layer. In most of its areas, there are 10-30 layers of stacked corneocytes with palms and soles having the most. Each corneocyte is surrounded by a protein envelope and is filled with water-retaining keratin proteins. The cellular shape and orientation of the keratin proteins add strength to the stratum corneum (Figure 2). [10]

When a formulation is applied onto the skin, several gradients are established across it, and drugs, to a certain extent, are able to pass through the stratum corneum. It is also reported that one important factor for drugs to permeate stratum corneum is the water gradient, which can be altered by application of several formulations onto the skin. [11] Hence for effective drug delivery through the skin, an external water gradient could be established.

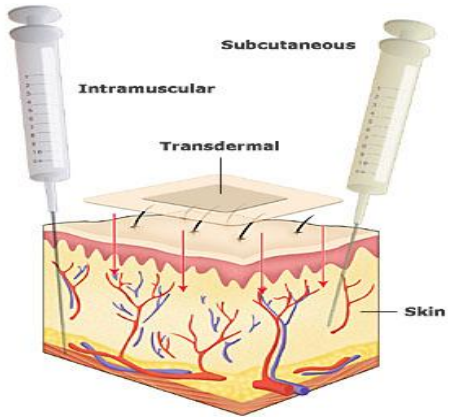

Figure 1: Drugs enter different layers of skin via intramuscular, subcutaneous, or transdermal delivery methods

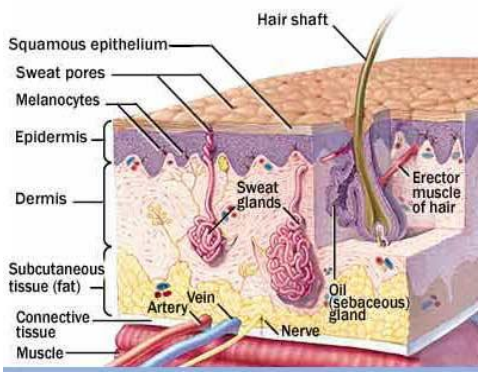

Figure 2: Structure of skin

Drugs, when applied onto the skin, can penetrate it via three major routes *viz*., through sweat glands, stratum corneum or hair follicles (Figure 3). [12] There has been a continuous effort for understanding the structural barrier and properties of stratum corneum. The permeation of drugs through hair follicles compared to the stratum corneum is also widely being discussed. [13] Further, it is reported that the follicular route is more favorable for permeation of polar molecules, as their influx through the stratum corneum is difficult. [14] There are specific factors which determine efficiency of drug permeation through the skin. The physicochemical nature of drug, site and condition of skin, the formulations, and their influence on the properties of stratum corneum are also important. [15]

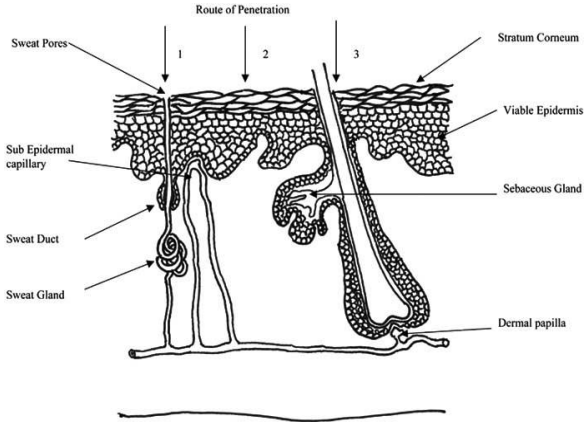

Figure 3: Skin showing routes of penetration: 1. through sweat ducts, 2. directly across stratum corneum and 3. By way of hair follicles

Entry of drugs through the skin mainly occurs through passive diffusion. In this context, Fick's law

of diffusion, states that rate of transfer of drugs across the membrane depends on drug solubility and also directly proportional to partition coefficient along with concentration of the diffusing substance, and inversely proportional to thickness of stratum corneum. This law of diffusion is given by

$$J = - D \frac{\partial C}{\partial t}$$

Where, J is the rate of transfer per unit area of the substance, C is the concentration of the diffusing substance, it is the thickness of the diffusing membrane (stratum corneum) and D is the partition coefficient. The negative sign indicates that permeation is in the direction of decreasing concentration, *ie*, down the concentration gradient. [16, 17]

FACTORS INFLUENCING TRANSDERMAL DRUG DELIVERY

Drug permeation across the skin is influenced by several physicochemical and biological parameters.

Physical factors: As discussed above, skin serves as a major barrier for the transdermal delivery of drugs. It has been observed that a wide range of molecules cannot easily diffuse through it. Micro needle array is a way to overcome this deficiency, especially for delivery of large macromolecules. The influence of micro needle geometry in enhancing penetration ability of drugs through the skin has been reviewed. [18] Effective skin permeability was calculated using different types of micro needles, by taking the effective permeability and thickness of skin into consideration. Most significant micro needle geometry, needed to achieve maximum penetration ability of large molecules through the skin was thus identified. Micro needle penetration depth seems to be the most important factor in determining the penetration efficacy.

Chemical factors

1. ***Molecular weight:*** Absorption is apparently inversely related to molecular weight, and smaller molecules are known to penetrate much faster than larger ones. The extent of drug penetration across the skin, based on their molecular weights, has been analysed and requirement of a coercive technique, like electroporation, has been established for high molecular weights drugs. [19] Hence greater the molecular weight, lower is the extent of penetration for obvious reasons.
2. ***Lipophilicity:*** Effect of partition coefficient on the diffusion of molecules has been studied. With reference to passive diffusion, increase in drug lipophilicity results in decreased permeation. [20] A similar study with nalbuphine and its prodrugs showed that increased lipophilicity leads to a decreased enhancement ratio. [21]
3. ***Formulations:*** Another factor which influences penetration of bioactive compounds across skin is the type of formulation designed for drug entry. Concentration of drugs affects their topical transport and thus formulations play a significant role in their skin entry. A correlation between their concentration and amount delivered through the skin has been arrived at. [22] Further, an increase in the formulation viscosity decreases drug penetration into the skin which may possibly be due to decreased diffusion.
4. ***Partition coefficient:*** Partition coefficient is considered to be an important factor for drug permeation through stratum corneum. For the former to penetrate through the latter, the drug should posses certain characteristics which include low molecular mass, ample solubility in oil, and a fairly high partition coefficient. It is observed that at higher partition coefficient values, the lipophilic drugs do not readily enter stratum corneum.

Certain biological factors elaborated below influence drug transport across the skin.

Skin conditions: Intact skin acts as a tough barrier but there are many agents which are known to damage it. Certain acids and alkalis injure barrier cells and thereby allow drug penetration. Diseases commonly alter skin conditions, which may increase drug permeability. In diseases characterized by damage to stratum corneum, the permeation further increases. As the first complete layer of new stratum corneum is being formed, the extent of permeation decreases. Maximum passive diffusion of drugs occurs in areas with abundant hair follicles than in areas with thicker stratum corneum.

Skin age: It is often assumed that skin of the young and elderly are more permeable than that of middle aged adults, but there is no conclusive evidence for this phenomenon. Children are more susceptible to some toxic effects of drugs and in premature infants, the stratum corneum is absent. This may be an

advantage for treating some diseases via topical applications.

Blood flow: Changes in peripheral circulation do not affect transdermal absorption. But an increased blood flow could reduce the time duration in which diffusing molecules remain in the dermis, simultaneously increasing concentration gradient across the skin. Local blood flow does not significantly affect assisted epidermal penetration of monovalent cations through the skin. [23] However, the penetration in case of diclofenac, salicylic acid and antipyrine was found to be enhanced by reduction of blood flow to the skin by use of phenylephrine, a vasoconstrictor. [24]

Skin metabolism: Several metabolic processes occur in the skin as a result of enzymes located in the epidermis which determine the therapeutic efficacy of topically applied drugs by modulating the skin biotransformations. [25]

METHODS FOR STUDYING TRANSDERMAL DRUG DELIVERY SYSTEMS

Studying the absorption of drugs onto the skin, following the route of drug permeation through stratum corneum, analyzing drug release kinetics and deciphering their pharmacokinetic profiles, are some methods by which transdermal drug delivery systems could be studied and monitored. Some *in vitro* and *in vivo* procedures for understanding these systems are described below.

In vitro methods: Excised skin from rats, mice, rabbits; monkeys, etc. have been used to study the diffusion of bioactive compounds through skin. Several diffusion cells have been employed for this purpose and the most widely preferred one is the Franz diffusion cell which has been used to study release of drugs. [26]

It is also found to be useful in assessing the bioequivalence of products applied topically to human excised skin. [27] Permeation of drugs like salicylic acid, cefazolin, naphazoline, urea, antipyrine and propranolol has been studied using excised skin of loach. [28]

As human skin is difficult to obtain and is texturally and compositionally variable, other artificial membranes are often employed to determine drug permeability. Some of these include silicone rubber, cellulose acetate, isopropyl myristate, etc. which serve as alternatives to stratum corneum. Isopropyl myristate is reported to be useful for analyzing percutaneous absorption of drugs, but it is also unpredictable without modifications. [29] Cellophane membrane has proved to be better than human cadaver membrane for absorption of diclophenac diethylamine in presence of menthol oil as penetration enhancer. [30]

***In vivo* methods**

1. ***Bioassays:*** Several specialized bioassays have been employed for testing topical formulations preceding clinical trials. Toxicological screening of various surfactants by measuring the degree of skin irritation has been reported with specific *in vivo* tests. [31] Similar studies with poloxamer gels, loaded with insulin and transdermally transferred into the system have been carried out for studying the efficacy of skin permeation. The procedure was found to be beneficial in lowering blood sugar levels. [32]

2. ***Microdialysis:*** Microdialysis probes are inserted into the dermis and perfused through inner layers. This is carried along by a buffer, where the drug passes from the extracellular fluids through buffers along the pores onto the membrane. Microdialysis has been proved to be an important technique for assessing percutaneous delivery of drugs. [33] This technique is mostly based on passive diffusion, where the bioactive compounds move down the concentration gradient through a semi permeable membrane. The main advantage here is that the extracellular concentration of drugs can be continuously monitored at different body compartments as the microdialysis probe can be implanted in any part of the body. [34] The method for assessment of transdermal drug bioavailability through microdialysis has been reviewed. [35]

Physical properties of skin: Some methods to study this include mechanical analysis, use of ultrasound waves, thermal determination through differential scanning calorimetry, use of Raman spectroscopy, etc. These techniques, especially the latter, examines outer layer of skin and also provides information related to hydration of stratum corneum. [36, 37] It also acts as an exclusive tool to determine skin moisturization. [35]

TRANSDERMAL THERAPEUTICS

The transdermal therapeutic system was introduced as a device that could deliver drugs through the skin at a controlled rate. Over a period of time, several of these have been employed to accomplish systemic circulation. This system provides a therapy for easy permeation of drugs through skin. [38]

Transdermal nitroglycerine: Systems used for delivery of nitroglycerine mainly focus on treatment of angina and congestive heart failure. The nitroglycerine patch is used for prophylactic treatment. [39] It was introduced for sustained release of drug. The effects of transdermal nitroglycerine on occurrence of ischemia have been reported. [40]

The frequency of ischemia was found to be increased during the off patch hours probably showing effective nitroglycerine absorption from the patch during "patch on" times. A similar study proved that transdermal delivery of nitroglycerine could be controlled by the transdermal delivery of ethanol [41] with both fluxes being linearly proportional.

Transdermal scopolamine: Scopolamine was the first transdermal patch to be marketed to treat motion sickness. Transdermal delivery of scopolamine in low doses was found to increase heart rate variability and also cardiac parasympathetic activity but on a short term basis. [42]The output on a long term basis is yet to be established. However, transdermal administration of this drug was totally ineffective clinically in case of asthma and chronic obstructive pulmonary disease. Additionally, it triggered many unwanted anticholinergic side effects.

Obviously the concentration of scopolamine used was not sufficient to attain the therapeutic levels at the cholinergic receptor site but was effective to trigger the anticholinergic side effects. [43] But the role of transdermal scopolamine on reducing postoperative nausea and vomiting has been significant. [44] It can be inferred that drug dosages are to be determined based on the required clinical treatment.

Transdermal clonidine: This type of formulation has been prepared for the treatment of hypertension and widely used as a result of its relatively smaller size and high potency. [2] Polymeric membranes have been employed for delivery of clonidine to achieve successful controlled release. [45] Transdermally administered clonidine has been reported to be very effective in the treatment of painful diabetic neuropathy. [46]

Transdermal nicotine: Wide ranges of nicotine patches are available, which are consequences of the intense market for smoking cessation therapy. Nicotine serves well as an ideal transdermal patch due to its low molecular weight, balanced coefficient and miscibility with water. [47] These patches help in decreasing withdrawal symptoms and promote sustained release of nicotine. [48] The effects of transdermal nicotine patches on memory and attention of male smokers and non smokers have been studied and it has been inferred that the patches enhance these qualities in non smokers but not in smokers. [49]

ENHANCING DRUG BIOAVAILABILITY

Most drugs do not readily penetrate the human skin. Several techniques are hence being developed to overcome the barrier for their efficient and smooth entry into and across the skin.

Ionotophoresis: The technique increases penetration rate of charged molecules through skin by application of an electrical gradient across it. For this purpose, an alternating current at a frequency of 12.5 to 2000 Hz is employed which results in significant penetration enhancement. [50, 51] Electric current decreases the electrical resistance of the skin thereby opening up its pores. The process is similar to that of electroporation, the effect of which increases with the extent of AC current. [52] Ionotophoresis is used in combination with laser Doppler perfusion imaging to study and monitor the physiology of skin as a result of pharmacological initiation. [53] Insights into the application of acetylcholine and sodium nitroprusside by this technique reveal that mechanisms different from prostaglandin production and sensory nerve activation at local levels may be involved in their transfer across the skin aided by the flow of blood. [54] Current intensity and vehicular composition are probably very important factors which control transdermal delivery of drugs as reported for ropinirole hydrochloride, [55] which is used in the therapy against Parkinson's disease. [56]

Electroporation: Electroporation creates pores across stratum corneum on the lipid bilayer by application of short electrical pulses which results in its high permeabilization thereby increasing penetration of bioactive compounds into the system. [57] The decrease in skin resistance leading to higher penetration effects is seen more in case of electroporation compared to ionotophoresis and in-depth study of possible mechanisms of stratum corneum perturbations by both these techniques may throw light, at least partially, on the possible

pathways by which drug transport may be favored across the skin. [58] Electrical field pulses used for this purpose vary depending upon the applications. The most frequently used pulse for drug delivery through skin is 0.5–1.0 V, which lasts for about 10 μs to ms, or more precisely, 1V per membrane for 1 ms pulse. [59] Some of the drugs that have been delivered transdermally through this technique are cyclosporine A, [60] tetracaine, [61] nalbuphine, [21] Timolol, [62] etc.

Piroxicam has been used in association with a surfactant for enhanced transdermal delivery. [63] Lipids would probably enhance the extent of electroporation as reported in case of insulin. [64] A special technique of in-skin electroporation using microneedle array for delivery of fluorescein isothiocyanate-dextran (model macromolecular drug) is more effective than conventional electroporation. [65]

Sonophoresis technique: Exposure to ultrasound waves (Sonophoresis) increases bioavailability of skin penetrating drugs by permitting movement of bioactive molecules through the skin. The frequency of waves may vary from a low 18-100 kHz to a higher range of about 3-10 MHz. [66] The drug entry may be enhanced in combination with other penetration enhancers, which provide a synergistic effect. [67] The technique works favorably for transdermal delivery of several compounds like heparin (using low frequency ultrasound), [68] caffeine, [69] insulin [70] and glucose. [71]

Penetration enhancers: Some sorption promoters/accelerants are known to weaken the stratum corneum and temporarily increase skin permeability thus acting as penetration enhancers. [72] There are several enhancers which are commonly used and the effect of these on human skin has been reported. [73] Oleic acid increases the permeation by fluidization of lipid layer of the stratum corneum as well as by lipid fluid separation. [74]

Similarly terpenes interact with intercellular stratum corneum lipids thereby increasing drug diffusivity. [75] 11, 12 and 18 carbon esters of N-acetylproline have been synthesized and used as chemical enhancers for benazepril and hydrocortisone. [76] A possible mechanism for increased drug penetration in the presence of enhancers could be complex formation between the two, as was proved by terpene based modeling studies. [77] Some of the other commonly used penetration enhancers are water, dimethylsulphoxide, azone, pyrrolidones, fatty acids, alcohols, fatty alcohols and glycols, surfactants, urea, essential oils, phospholipids, etc. [78]

Liposomes: Colloidal particles, consisting of phospholipids and cholesterol, *viz.* liposomes have been tried for drug encapsulation and also for their efficient penetration through the skin. [79] The charged lipids present in them possibly promote efficient penetration. [80]The transdermal delivery of tea catechins encapsulated in liposomes is further enhanced by incorporating anionic surfactants in the presence of ethanol. [81] They are also effective in the delivery of ketotifen into the skin. [82] Liposomes have shown considerable potential in the delivery of Indinavir, a protease inhibitor used in HIV treatment. This drug, due to its short biological half life and extensive first pass metabolism cannot be administered orally. Ethanolic liposomes have been successful in delivering this drug transdermally. [83] Their use as transdermal drug delivery systems has been reviewed. [84]

SKIN FORMULATIONS

Skin formulations currently in use range from powders to semisolids and liquids. These are generally prepared to increase drug bioavailability by taking into account their stability and drug compatibility. Further, the properties of these vehicles affect tolerability and efficacy of topical agents. [85] Formulations in the form of creams, ointments, foam, lotion, etc, are shown to improve pharmacokinetic property of drugs along with increasing bioavailability. [86] Some of the commonly used formulations are discussed below.

Gels: These semi solid systems, which are cross linked to form a continuous structure similar to that of a solid, are of different type's *viz.*, hydrogels, organogels, xerogels etc. Their synthesis usually involves a gelling agent. Recently, polymer gels are in focus as film forming agents in the transdermal delivery of drugs. [87] Studies are being carried out to investigate efficacy of drug permeation using gels as delivery vehicles which possess several advantages like lesser irritation, improved cosmetic appearance, non greasy feel, etc. [88] Hybrid gels have been formulated for their applications as bioadhesive films. [89] Carbopol gels are investigated for their role in the delivery of triamcinolone acetonide acetate. [90] Novel specific formulations of pharmacogels have proved to be very effective in the delivery of propranolol hydrochloride transdermally. [91] Recently, nanogels as vehicles for the topical drug delivery have shown great promise. Their development and applications in drug delivery have been reviewed. [92]. Anti-inflammatory effects due to topical applications of triamcinolone acetonide gel have also been reported. [93]

Ointments: These greasy, semisolid preparations, where the bioactive molecules are dissolved or dispersed in the medium are of different types, *viz.*, hydrocarbon bases, oils, emulsions, silicones, Bases involving vegetable as well as synthetic oils are frequently employed as dermatological vehicles. Silicones, which are synthetic polymers known for their medicinal properties have been used in topical formulations as an oil gel base in the delivery of drugs. [94] The use of these bases dates back to 1960s, where mineral oil gels were prepared by simple procedures and employed as bases for transdermal delivery of drugs. [95]

Emulsions have been explored for their efficiency in drug delivery by the same route. The application of emulsions in drug delivery is a current area of interest. [96] Microemulsions have been used in transdermal delivery of testosterone. [97] Recent studies involve the use of nanoemulsions, as they possess several advantages when compared to that of microemulsions. The efficacy of nanoemulsions in topical delivery of drugs has been reviewed. [98] Nanoemulsions range from 20-500 nm, stabilized by surfactants [99] and utilized for delivery of drugs like progesterone and caffeine. [100, 101]

Several other formulations have been used, *viz.*, creams, which are semi solid emulsions, liquid preparations, like lotions, tinctures, ear drops, etc. which are known to maintain their moisture content, pastes, which are ointments that are 50% powder dispersed in fatty bases, and aerosols that function as drug delivery systems for solutions, suspensions and emulsions. All these formulations are tailor made as required for specific applications.

CONCLUSION

Transdermal system is an important route for drug delivery due to its several advantages when compared to other modes. It is particularly useful for the delivery of drugs that are prone to be destroyed by the liver when taken orally. Skin, however, acts as a major barrier to this process. Several physicochemical and biological factors influence assimilation through this route, and these are known to affect the efficacy of drugs penetrating the skin. There are also several strategies put forth to increase the permeation efficiency of drugs through the skin, which include use of permeation enhancers, and certain techniques such as sonophoresis, ionotophoresis, etc. Currently a number of clinical trials are under progress to determine the bioavailability of skin penetrating drugs. There is a strong possibility of this route becoming the pathway of choice for effective drug delivery in future.

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