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TRANSDERMAL DRUG DELIVERY SYSTEM: A REVIEW

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Various new technologies have been developed for the transdermal delivery of some important drugs. Physical and chemical means of crossing the lipophilic stratum corneum, the outermost layer of the skin, are being explored. A thorough understanding of skin physiology and the basics behind the new technologies would be useful for understanding these exciting new drug delivery systems. Alternative techniques of physical sciences including electrical signals, ultrasonic and laser radiations are being used to facilitate delivery of drugs across the epidermal barrier. Several approaches in form of carriers/ vehicles are also being developed for efficient delivery of drugs. Another major concern is regulatory issues of transdermal products to be launched in the market.
This review deals with a brief insight on physiological properties of the skin, several techniques for drug permeation enhancement and regulatory issues over transdermal drug delivery.

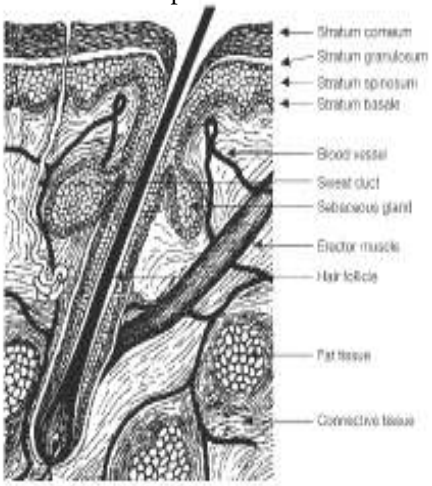
Keywords : TEWL, Iontophoresis, Electroporation, Sonophoresis, Microemulsion, Nanoemulsion, Nanoparticles, Liposomes, Niosome, Ethosome, Transferosome.

INTRODUCTION

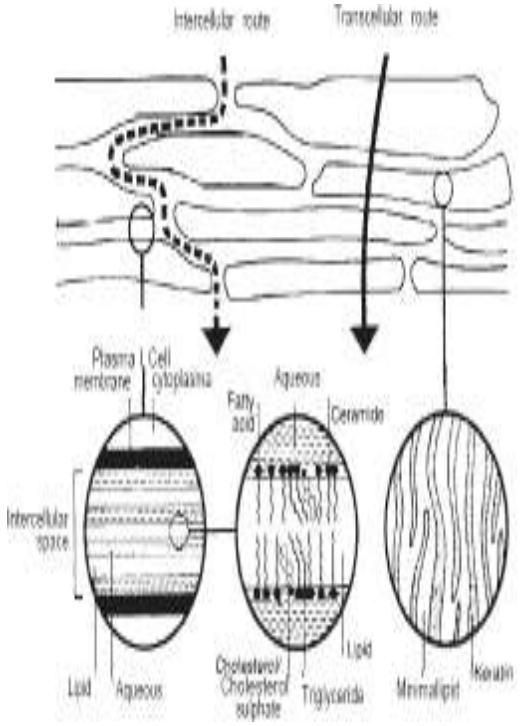
FDA approved the first transdermal patch products in 1981. These delivery systems provided the controlled systemic absorption of scopolamine for the prevention of motion sickness (*Transderm-Scop*, ALZA Corp.) and nitroglycerine for the prevention of angina pectoris associated with coronary artery disease (Transderm-Nitro). Over the last two decades, more than 35 transdermal products have been approved generating sales of $3.2 billion in 2002, which is predicted to rise to $4.5 billion in 2008. More recently, such dosage forms have been developed and/or modified in order to enhance the driving force of drug diffusion (thermodynamic activity) and/or increase the permeability of the skin. These approaches include the use of penetration enhancers, supersaturated systems, prodrugs, liposomes and other vesicles.

ROUTES OF PENETRATION

Under normal circumstances, the predominant route is through the intercellular spaces.[1-5]



Transverse Section of Skin



Possible routes for drug penetration

The predominant route is via intercellular spaces. The diffusional pathlength is therefore much longer than the simple thickness of the stratum corneum (~20 mm) and has been estimated as long as 500 mm. Importantly, the intercellular spaces contain structured lipids and a diffusing molecule has to cross a variety of lipophilic and hydrophilic domains before it reaches the junction between the stratum corneum and the viable epidermis.[1-5]

The transepidermal route across the continuous stratum corneum comprises transport via intracellular and intercellular spaces. The polar molecules mainly diffuse through the polar pathway consisting of "boundwater"

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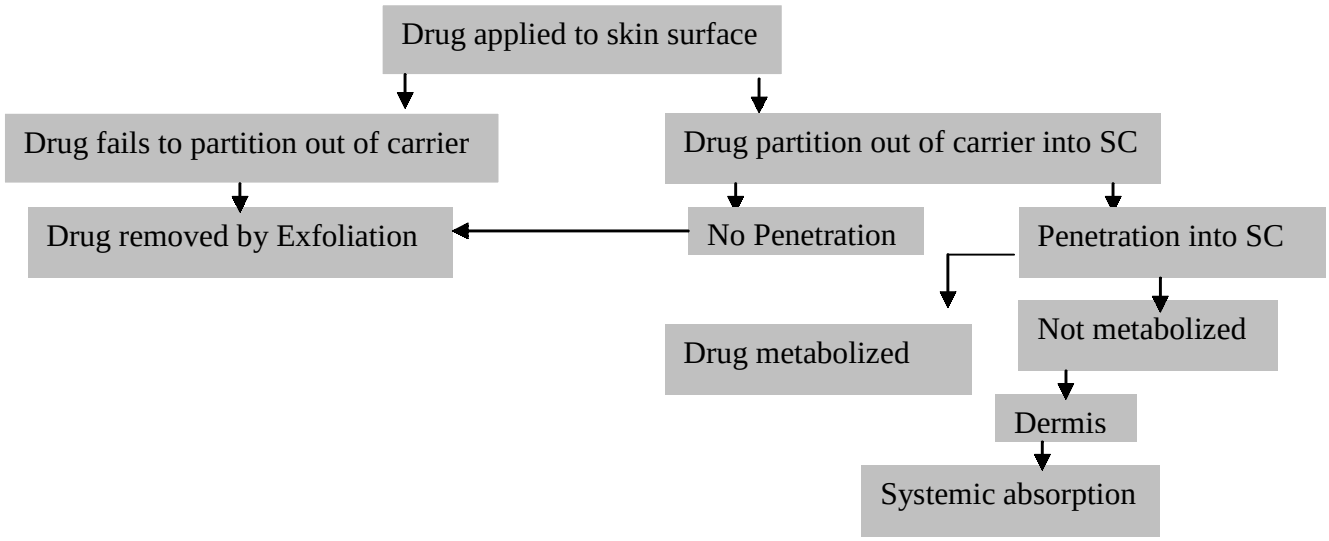
within the hydrated stratum corneum, whereas the non-polar molecules dissolve and diffuse through the non-aqueous lipid matrix of the stratum corneum. The transappendageal route transports substances via the sweat glands and the hair follicles with their associated sebaceous glands, but it is considered to be of minor importance because of relatively smaller area (less than 0.1% of total surface).

BODY PART

The most permeable areas are the mucous membranes, scrotal skin, and eyelids while face/head, chest/back, buttocks, abdomen, and upper arms/legs shows intermediate permeability. The least permeable areas are the palmar /plantar surfaces and nails

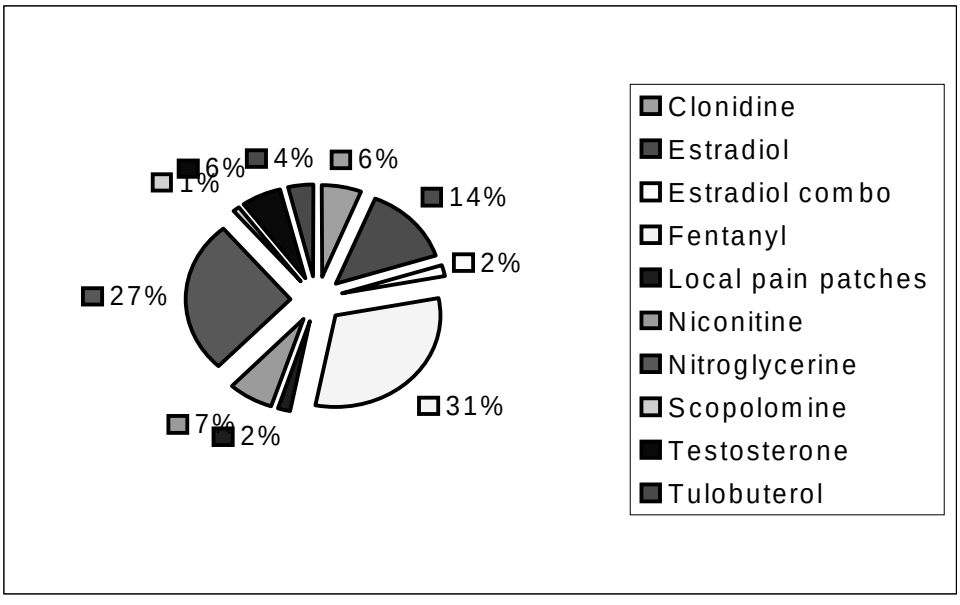


FACTORS AFFECTING PERMEABILITY OF STRATUM CORNEUM

Human skin is not all the same. There are numerous differences among patient groups as well as between various regions of the body, age and ethnicity.

SKIN STATUS OR CONDITIONS

- Hydration: Hydrated skin is more permeable than dry skin.
- Broken or irritated skin: Drugs can more easily bypass the stratum corneum, increases permeability.
- Temperature: Warmer skin is more permeable.



SOME TRANSDERMAL PRODUCTS

Product name	Drug	Manufacturer	Indication
Alora	Estradiol	TheraTech/Proctol and Gamble	Postmenstrual syndrome
Androderm	Testosterone	TheraTech/GlaxoSmithKline	Hypogonadism (males)
Catapres-TTS	Clonidine	Alza/Boehinger Ingelheim	Hypertension
Climaderm	Estradiol	Ethical Holdings/Wyeth-Ayerest	Postmenstrual syndrome
Climara	Estradiol	3M Pharmaceuticals/Berlex Labs	Postmenstrual syndrome
CombiPatch	Estradiol/Norethindrone	Noven , Inc./Aventis	Hormone replacement therapy
Deponit	Nitroglycerin	Schwarz-Pharma	Angina pectoris
Duragesic	Fentanyl	Alza/Janssen Pharmaceutica	Moderate/severe pain
Estraderm	Estradiol	Alza/Norvatis	Postmenstrual syndrome
Fematrix	Estrogen	Ethical Holdings/Solvay Healthcare Ltd.	Postmenstrual syndrome
FemPatch	Estradiol	Parke-Davis	Postmenstrual syndrome
Habitraol	Nicotine	Novartis	Smoking cessation
Minitran	Nitroglycerin	3M Pharmaceuticals	Angina pectoris
Nicoderm	Nicotine	Alza/GlaxoSmithKline	Smoking cessation
Nicotrol	Nicotine	Cygnus Inc./McNeil Consumer Products, Ltd.	Smoking cessation
Nitrodisc	Nitroglycerin	Roberts Pharmaceuticals	Angina pectoris
Nitro-dur	Nitroglycerin	Key Pharmaceuticals	Angina pectoris
Nuvelle TS	Estrogen/Progesterone	Ethical Holdings/Schering	Hormone replacement therapy
Ortho-Evra	Norelgestromin/estradiol	Ortho-McNeil Pharmaceuticals	Birth control
Prostep	Nicotine	Elan Corp./Lederle Labs	Smoking cessation

- Sunburn: Initially skin is less permeable; after peeling, it becomes more permeable.
- Eczema/ Psoriasis: Regions exhibit increased/ decreased permeability.
- Skin peels: Removal of the stratum corneum increases permeability.

DRUG

For developing a transdermal drug delivery system, the drug has to be chosen with great care. Following are some of the desirable properties of a drug suitable for transdermal delivery.

- The drug should have a molecular weight less than approximately 1000 daltons.
- The drug should have affinity for both – lipophilic and hydrophilic phases. Extreme partitioning characteristics are not conducive to successful drug delivery via the skin.
- The drug should have low melting point.

Along with these propertie sthe drug should be potent, having short half life and be non irritating.

ADHESIVES

The fastening of all transdermal devices to the skin has so far been done by using a pressure sensitive adhesive which can be positioned on the face of the device or in the back of the device and extending peripherally. Both types of adhesive system should fulfill the following criteria -

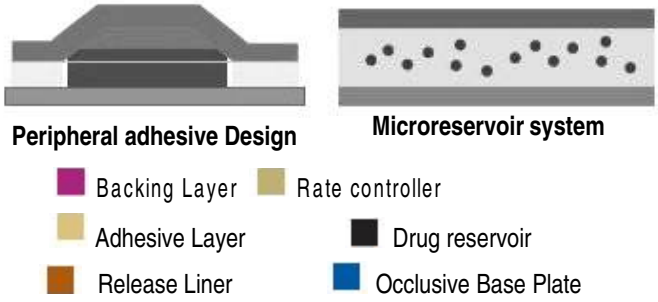
- Should adhere to the skin aggressively, should be easily removed.
- Should not leave any unwashable residue on the skin.
- Should not irritate or sensitize the skin.

The face adhesive system should also fulfill the following criteria.

- Physical and chemical compatibility with the drug, excipients and enhancers of the device of which it is a part.
- Permeation of drug should not be affected.
- The delivery of simple or blended permeation enhancers should not be affected.

TYPES OF TRANSDERMAL DELIVERY SYSTEMS

Reservoir System Matrix Dispersion System



RESERVOIR SYSTEMS

In this system, the drug reservoir is embedded between an impervious backing layer and a rate controlling membrane. The drug releases only through the rate-controlling membrane, which can be microporous or nonporous.

In the drug reservoir compartment, the drug can be in the form of a solution, suspension, or gel or dispersed in a solid polymer matrix. On the outer surface of the polymeric membrane a thin layer of drug-compatible, hypoallergenic adhesive polymer can be applied.

MATRIX SYSTEMS

Drug-in-adhesive system

The drug reservoir is formed by dispersing the drug in an adhesive polymer and then spreading the medicated polymer adhesive by solvent casting or by melting the adhesive (in the case of hot-melt adhesives) onto an impervious backing layer. On top of the reservoir, layers of unmedicated adhesive polymer are applied.

Matrix-dispersion system

The drug is dispersed homogeneously in a hydrophilic or lipophilic polymer matrix. This drug containing polymer disk then is fixed onto an occlusive base plate in a compartment fabricated from a drug-impermeable backing layer. Instead of applying the adhesive on the face of the drug reservoir, it is spread along the circumference to form a strip of adhesive rim.

MICRO-RESERVOIR SYSTEMS

This drug delivery system is a combination of reservoir and matrix-dispersion systems. The drug reservoir is formed by suspending the drug in an aqueous solution of water-soluble polymer and then dispersing the solution homogeneously in a lipophilic polymer to form thousands of unleachable, microscopic spheres of drug reservoirs. The thermodynamically unstable dispersion is stabilized quickly by immediately cross-linking the polymer in situ.

PERMEATION ENHANCERS

MECHANICAL METHODS

The various classes of active systems under development include iontophoresis, electroporation, microneedles, abrasion, needle-less injection, suction, stretching, ultrasound, magnetophoresis, radio frequency, lasers, photomechanical waves, and temperature manipulation. Some most commonly employed techniques include the following.

a. Iontophoresis: This method involves the application of a low level electric current either directly to the skin or indirectly via the dosage form in order to enhance permeation of a topically applied therapeutic agent.[6-9] Increased drug permeation as a result of this methodology can be attributed to either one or a combination of the following mechanisms: Electro-repulsion (for charged solutes), electro-osmosis (for uncharged solutes) and electro-pertubation (for both charged and uncharged).

b. Electroporation: This method involves the application of high voltage pulses to the skin that has been suggested to induce the formation of transient pores. High voltages (•100 V) and short treatment durations (milliseconds) are most frequently employed. The technology has been successfully used to enhance the skin permeability of molecules with differing lipophilicity and size (i.e. small molecules, proteins, peptides and oligonucleotides) including biopharmaceuticals with molecular weights greater that 7kDA.

c. Microneedle-based Devices: The very first microneedle systems, described in 1976, consisted of a drug reservoir and a plurality of projections (microneedles 50 to 100 mm long) extending from the reservoir, which penetrated the stratum corneum and epidermis to deliver the drug.[10]

d. Skin Abrasion: The abrasion technique involves the direct removal or disruption of the upper layers of the skin to facilitate the permeation of topically applied medicaments. Some of these devices are based on techniques employed by dermatologists for superficial skin resurfacing (e.g. microdermabrasion) which are used in the treatment of acne, scars, hyperpigmentaion and other skin blemishes.

e. Needle-less Injection: Transdermal delivery is achieved by firing the liquid or solid particles at supersonic speeds through the outer layers of the skin using a suitable energy source. The mechanism involves forcing compressed gas (helium) through the nozzle, with the resultant drug particles entrained within the jet flow reportedly traveling at sufficient velocity for skin penetration.

f. Ultrasound (sonophoresis and phonophoresis): This technique involves the use of ultrasonic energy to enhance the transdermal delivery of solutes either simultaneously or via pre-treatment. It uses low frequency ultrasound (55 kHz) for an average duration of 15 seconds to enhance skin permeability.[11]

g.Laser Radiation: This method involves direct and controlled exposure of a laser to the skin that results in the ablation of the stratum corneum without significantly damaging the underlying epidermis. Removal of the stratum corneum using this method has been shown to enhance the delivery of lipophilic and hydrophilic drugs.[12]

CARRIERS/ VEHICLES

a. Micro or nanocapsules

These are composed of multiple concentric bilayers of surfactant; separated by a polar liquid medium, generally water in which the hydrophilic additives can be incorporated. Their lipid core allows encapsulation of lipid additives and their multi-lamellar (lipid/water) structure creates good skin affinity leading to cutaneous penetration and good hydration.

b. Nanoemulsions/ Sub-micron emulsions (SMEs)/ Mini-emulsions

These are oil-in-water emulsions with an average droplet size ranging from 100 to 500 nm. They have very good stability and they do not undergo phase separation during storage. They have a liquid lipophilic core and are appropriate for lipophilic compound transportation. Many studies showed reduced transepidermal water loss, which means support to the barrier function of the skin.[13] Nanoemulsion viscosity is very low, which is interesting because they can be produced as sprays,

c. In solid lipid nanoparticles (SLNs)

These droplets are made by solid lipids.[14] Their sizes range from 50 to 1000 nm. They can also be stabilised by surfactants or polymers. There are mainly three structures: Homogeneous matrix, drug-enriched shell and drug-enriched core. They can protect active components against chemical degradation and modulate compound release. SLNs also present occlusive properties because of the formation of a film on the skin. This film formed by lipid fusion is supposed to be a pore-less film with improved skin hydration and protection properties.

d. Multiple emulsions

These W/O/W emulsions consist in the dispersion of a W/O emulsion in an aqueous phase under several conditions. [15] One can incorporate different water-soluble ingredients (even if they are incompatible) and also oil soluble additives. Like SLNs, these substances will be protected and release sustained by controlling droplet breakdown. These systems can have high oily phase

contents (65%, Trixera, Bain emollient, Avène) and thus present good hydration. Their efficacy has been demonstrated in dermatology to treat stretch marks (Triffadiane, CS Dermatologie).

e. Microemulsions

These formulations have been shown to be superior for cutaneous delivery compared to other conventional vehicles. [16] These systems are identified as transparent mixtures of water, oil and surfactants. They are thermodynamically stable and optically isotropic. Microemulsions are spontaneously produced in a narrow range of oil-water-surfactant composition, represented on pseudo-ternary diagram phases. They are dynamic systems with continuously fluctuating interfaces. Their good dermal and transdermal delivery properties could be attributed to their excellent solubilising properties.

Their high solubilising properties improve biodispen sibility and thus reduce the efficient dose thereby increasing tolerability. Furthermore, their restructuring effect on skin and hair (due to their high lipid content) make microemulsion formulations adapt to altered skin and hair conditions.

f. Vesicular carriers

Liposomes: These are colloidal particles formed as concentric biomolecular layers that are capable of encapsulating drugs. Their delivery mechanism is reported to be associated with accumulation of the liposomes and associated drug in the stratum corneum and upper skin layers, with minimal drug penetrating to the deeper tissues and systemic circulation. It is interesting that the most effective liposomes are reported to be those composed of lipids similar to stratum corneum lipids,[17] which are most likely to enter stratum corneum lipid lamellae and fuse with endogenous lipids.

Niosomes: These are vesicles composed of nonionic surfactants that have been evaluated as carriers for a number of drug and cosmetic applications. This carrier has more permeability than liposomes for transdermal drug delivery.

Transfersomes: These are vesicles composed of phospholipids as their main ingredient with 10-25% surfactant (such as sodium cholate) and 3-10% ethanol. The surfactant molecules act as "edge activators", conferring ultradeformability on the transfersomes, which reportedly allows them to squeeze through channels in the stratum corneum that are less than one-tenth the diameter of the transfersome.

Ethosomes: These are liposomes with high alcohol content capable of enhancing penetration to deep tissues and the systemic circulation.[18-21] It is proposed that alcohol fluidises the ethosomal lipids and stratum corneum bilayer lipids thus allowing the soft, malleable ethosomes to penetrate.

3. MISCELLANEOUS TECHNIQUES

a. Prodrugs and Ion-Pairs

The prodrug approach has been investigated to enhance dermal and transdermal delivery of drugs with unfavourable partition coefficients.[22] The prodrug design strategy generally involves addition of a pro-moiety to increase partition coefficient and solubility to increase the transport of the drug in the stratum corneum. Upon reaching the viable epidermis, esterases release the active drug by hydrolysis thereby optimising concentration in the epidermis.

Charged drug molecules do not readily partition into or permeate through human skin. Formation of lipophilic ionpairs has been investigated to increase stratum corneum penetration of charged species. This strategy involves adding an oppositely charged species to the charged drug, forming an ion-pair in which the charges are neutralised so that the complex can partition into and permeate through the stratum corneum. The ion-pair then dissociates in the aqueous viable epidermis releasing the parent charged drug that can diffuse within the epidermal and dermal tissues.

b. Vehicle – Saturated and Supersaturated Solutions:

The maximum skin penetration rate is obtained when a drug is at its highest thermodynamic activity as is the case in a supersaturated solution. Supersaturated solutions can occur due to evaporation of solvent or by mixing of cosolvents.

c. Eutectic Systems:

The melting point of a drug influences solubility and hence skin penetration. According to solution theory, lower the melting point, greater the solubility of a material in a given solvent, including skin lipids. The melting point of a drug delivery system can be lowered by formation of a eutectic mixture, which is a binary system. At a constant ratio, the components inhibit the crystallization process of each other, such that the melting point of the two components in the mixture is less than that of each component alone.

d. Complexes:

Complexation of drugs with cyclodextrins has been used to enhance aqueous solubility and drug stability. Cyclodextrins of pharmaceutical relevance contain 6, 7 or 8 dextrose molecules bound in a 1,4- configuration to form rings of various diameters. The ring has a hydrophilic exterior and lipophilic core in which appropriately sized organic molecules can form non-covalent inclusion complexes resulting in increased aqueous solubility and

chemical stability.

Cyclodextrins are large molecules, with molecular weights greater than 1000 Da, therefore it would be expected that they would not readily permeate the skin. Complexation with cyclodextrins has been variously reported to both increase and decrease skin penetration.[23-24]

REGULATORY STRATEGY FOR INVESTIGATIONAL NEW DRUG (IND) APPLICATION AND NEW DRUG APPLICATION SUBMISSIONS FOR TDDS

- Standard irritation and sensitization studies should be performed with the patch itself in animals/ humans.
- Negotiate the timing and implementation of the toxicology requirements.
- The dermatology division at FDA should review dermal aspects of the IND and New drug Application (NDA).
- Primary review should occur at the division that handles the indication under study.
- Dose ranging studies be required in Phase 2.
- Single Phase 3 study could be negotiated.

CONCLUSION

Successful transdermal drug delivery requires numerous considerations owing to the nature and function of the site of application. It should always be kept in mind, that the basic functions of the skin are protection and containment. As per these rulings, it would seem exceptionally difficult to cross the skin for systemic absorption. However, with continuous exploration of the structure, function and physicochemical propertties of the skin, more and more new drug products are being developed for transdermal delivery. The safe and effective drug delivery is the ultimate target for each and every new technology ever explored.

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