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Research Article

A Review on Transdermal Drug Delivery

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ABSTRACT

Human beings have been placing salves, lotions and potions on their skin from ancient times and the concept of delivering drugs through the skin is a practice, which dates as far back as the 16th century BC. In the late seventies transdermal drug delivery (TDD) was heralded as a methodology that could provide blood drug concentrations controlled by a device and there was an expectation that it could therefore develop into a universal strategy for the administration of medicines. This review is collection about knowledge about this drug delivery system.

Keywords: Transdermal drug delivery, administration, blood drug concentrations.

INTRODUCTION

The transdermal route of controlled drug delivery is often dismissed as a relatively minor player in modern pharmaceutical sciences. One commonly hears that the skin is too good a barrier to permit the delivery of all but a few compounds and that transdermal transport is not even worth the consideration for new drugs of the biotechnology industry ¹⁻⁴. This has however been disputed as today TDD is a well-accepted means of delivering many drugs to the systemic circulation² in order to achieve a desired pharmacological outcome. Traditional preparations used include ointments, gels, creams and medicinal plasters containing natural herbs and compounds. The development of the first pharmaceutical transdermal patch of scopolamine for motion sickness in the early 1980s heralded acceptance of the benefits and applicability of this method of administration of modern commercial products ^{4 - 6}. The success of this approach is evidenced by the fact that there are currently more than 35 TDD products approved in the USA for the treatment of conditions including hypertension, angina, female menopause, severe pain states, nicotine dependence, male hypogonadism, local pain control and more recently, contraception and urinary incontinence ^{2,8}. Several products are in late-stage development that will further expand TDD usage into new therapeutic areas, including Parkinson's disease, attention deficit and hyperactivity disorder and female dysfunction ^{5,6}. New and improved TDD products are also under development that will expand the number of therapeutic options in pain

management, osteoporosis and hormone replacement⁶. The current USA market for transdermal patches is over \$3 billion annually and for testosterone gel is approximately \$225 million ^{7,8,13} and represents the most successful non-oral systemic drug delivery system ¹⁷.

Rationale For Transdermal Drug Delivery

The skin offers such an excellent barrier to molecular transport, the rationale for this delivery strategy needs to be carefully identified. There are several instances in which the most convenient of drug intake methods (the oral route) is not feasible therefore alternative routes must be sought. Although intravenous introduction of the medicament avoids many of these shortfalls (such as gastrointestinal tract (GIT) and hepatic metabolism), its invasive nature (particularly for chronic administration) has encouraged the search for alternative strategies and few anatomical orifices have not been investigated for their potential as optional drug delivery routes. The implementation of TDD technology must be therapeutically justified. Drugs with high oral bioavailability and infrequent dosing regimens that are well accepted by patients do not warrant such measures. Similarly, transdermal administration is not a means to achieve rapid bolus-type drug inputs, rather it is usually designed to offer slow, sustained drug delivery over substantial periods of time and, as such, tolerance-inducing drugs or those (e.g., hormones) requiring chronopharmacological management are, at least to date, not suitable. Nevertheless, there remains a

large pool of drugs for which TDD is desirable but presently unfeasible. The nature of the stratum corneum (SC) is, in essence, the key to this problem. The excellent diffusional resistance offered by the membrane means that the daily drug dose that can be systematically delivered through a reasonable ‘patch-size’ area remains in the < 10 mg range¹⁷.

Advantage of TDDS Over Conventional Dosage Form

Transdermal drug delivery offers several important advantages over more traditional dosage forms steady permeation of drug across the skin allows for more consistent serum drug levels, which is often the goal of the therapy. Lack of peaks in plasma concentration reduces the risk of side effects. So drugs those require relatively consistent plasma levels are good candidate for transdermal drug delivery. If toxicity were to develop from drug administered transdermally, the effect could be limited by removing the patch. It's convenience such as simple dosing regimen can lead to patient's adherence to drug therapy. Transdermal delivery can be used as alternate route of administration to accommodate patient who are nauseated or unconscious. Drugs that cause gastrointestinal upset are good candidates for transdermal delivery because this method avoids direct effect on the stomach and intestine. Drugs that are degraded by enzyme and acid are also good candidate for transdermal delivery system. First pass metabolism. An additional limitation to oral drug delivery can be avoided with transdermal administration. Minimize intra and inter patient variation and Self administration is possible²¹.

Disadvantages of TDDS

- Stratum corneum provides rate-limiting steps.
- Possibility of local irritation at the site of application, erythema, itching and local edema can be caused by the adhesive, or the other excipient in the patch.
- Patient develops severe allergic reaction to transdermal patches, and in this case therapy must be discontinued.
- Skin's low permeability limits the number of drugs that can be delivered in this manner.
- Drugs with hydrophilic structure permeate the skin too slowly to be of therapeutic benefit.
- In order to maintain consistent release rate, transdermal patches contains surplus of active molecule, as stable concentration gradient is the mechanism used to maintain consistent release rate.
- Damage of the patches, particularly membrane or reservoir patch can result in

poor control over release rate. The release rate from a damage patch would more likely to be controlled by the skin than the patch, resulting in a higher perhaps toxic rate of drug delivery.

Innovations in Transdermal Drug Delivery

TDDS has been the subject of extensive research¹¹. The introduction of new transdermal technologies such as chemical penetration enhancement^{2-6,9,11,12,15,18,19,20} iontophoresis^{2-6,7,11,15,16,18,19} sonophoresis^{2-7,10-12,14,15,19} transfersomes¹², thermal energy^{6,8}, magnetic energy⁶, micro needle applications^{6,8}, electroporation^{3,4,7,11,12,19} and high velocity jet injectors⁸challenge the paradigm that there are only a few drug candidates for TDD. Despite difficult issues related to skin tolerability and regulatory approval, most attention, at least until recently, has been directed at the use of chemical penetration enhancers. However, this focus is now shifting towards the development of novel vehicles comprising accepted excipients (including lipid vesicular-based systems, supersaturated formulations and micro emulsions) and to the use of physical methods to overcome the barrier. In the latter category, iontophoresis is the dominant player and is by far the method furthest along the evaluatory path. Applications of electroporation, ultrasound and high pressure, etc., remain at the research and feasibility stage of development. Interestingly, the level of endeavor devoted to either removal or perforation of the SC (e.g., by laser ablation, or the use of micro needle arrays) has increased sharply, with these so-called ‘minimally invasive’ techniques essentially dispensing with the challenge of the barrier function of the skin²¹. Physical methods have the advantage of decreased skin irritant/allergic responses, as well as no interaction with the drugs being delivered¹¹. The extent to which these are translated into practice will be defined by time¹². TDDS is therefore a thriving area of research and product development, with many new diverse technology offerings both within and beyond traditional passive transdermal technologies⁶.

The Skin Barrier

Human skin has a multifunctional role, primary among which is its role as a barrier against both the egress of endogenous substances such as water and the ingress of xenobiotic material (chemicals and drugs). This barrier function of the skin is reflected by its multilayered structure. The top or uppermost layer of the skin known as the stratum corneum (SC). The SC is also known to exhibit selective permeability and allows only relatively lipophilic compounds to diffuse into the lower layers. As a result of the dead nature of the SC, solute transport across this layer is primarily by passive diffusion in

accordance with Fick's Law and no active transport processes have been identified.

The stratum corneum

This is the most superficial layer of the epidermis and represents the specialized end product of keratinization; it is the single most important structure responsible for barrier function in the skin. The stratum corneum is made up of flat, plate-shaped cells 30 μ wide and 0.8 μ deep, closely applied to each other on all sides and interconnected by many desmosomes. These cells, also known as corneocytes, are anucleate and metabolically inert, and contain many longitudinally arranged fibroustono filaments in between which an amorphous matrix and remnants of cellular organelles are found. Since the whole layer is 15 to 20 cell layers deep, its total thickness averages 15 μ . An important feature of these cells is the thickness of their membranes. Unlike the plasma membrane of the viable cells of the epidermis (75 to 100 Å), that of cells of the stratum corneum measures approximately 200 Å. However, it retains the structural features of a biomembrane as described by Singer, being composed of a viscous lipid bilayer in which globular proteins are interspersed. In certain areas these mobile globular proteins extend all the way through the lipid phase; it is postulated that 10° Å pores are formed between such proteins at sites of aggregation, establishing a connection between both sides of the membrane. Although lipids make up only 5% of the chemical composition of total hydrated stratum corneum, they represent the major constituent of the cell membrane and impart to it its distinctive characteristics of semi permeability. Physiologically, the stratum corneum behaves like a composite membrane, this derives from the fact that the first structure encountered by a diffusing molecule is the plasma membrane of the corneocytes, and since lipids are major constituents of this membrane, it follows that the lipid solubility of this diffusing molecule will be important in determining its entry and transport through the stratum corneum. Thus, this layer can absorb approximately six times its own weight in water, and in doing so will increase in thickness from 15 to 45 μ . This property of water binding is related to increased permeability to diffusing molecules. It is now well established that the rate-limiting barrier of the epidermis resides in the stratum corneum, or horny layer, and that diffusion of molecules through this layer is purely passive. As such, this process does not require expenditure of metabolic energy; in fact, dead epidermis is as effective a barrier as live tissue. Furthermore, it has been demonstrate that diffusion characteristics through stratum corneum remain the same irrespective of the direction of transport. These observations have allowed extensive in vitro studies, leading to a

better understanding of the physicochemical dynamics involved in percutaneous absorption. As mentioned, the stratum corneum is an effective two-way barrier, but is not a complete one and does allow selective transport of some molecules from the surface into the viable epidermis. Percutaneous absorption and therefore pharmacological effectiveness of topically applied medications are based on this property. The rate of diffusion may be negligibly low or relatively high depending on a variety of factors which will be discussed below. Once transport across the stratum corneum has taken place, there is little impediment to transport across the remainder of the epidermis into the dermis ²³.

Drug Delivery Routes Across Human Skin

Drug molecules in contact with the skin surface can penetrate by three potential pathways: through the sweat ducts, via the hair follicles and sebaceous glands (collectively called the shunt or appendageal route), or directly across the stratum corneum.

The Process-Percutaneous Absorption

The stratum corneum is considered not only as the main barrier to skin penetration but also as a major permeation pathway from topical and transdermal delivery systems. The stratum corneum is made up of tightly packed, semi-crystalline intercellular lipid domains and its extremely compact corneocytes create a barrier highly resistant to percutaneous transport ^{25,26}. The lipid layer of the stratum corneum has been described as a possible pathway for transport of hydrophobic substances, whereas the polar heads of lipids represent a relatively hydrophilic pathway ²⁷. The proposed transport pathways in the stratum corneum have been well defined. However, the existence of appendage pathways for percutaneous absorption remains unclear and is often disregarded. Literature reports suggest that the pilosebaceous unit (hair follicle, hair shaft and sebaceous gland) may contribute significantly to topical and transdermal delivery in addition to the transepidermal route ^{28,29,30}. Fig.4 illustrates the percutaneous absorption of drug applied on the skin surface.

Type of Transdermal Delivery

Human skin serves a protective function by imposing physicochemical limitations to the type of permeant that can traverse the barrier. For a drug to be delivered passively via the skin it needs to have a suitable lipophilicity and a molecular weight < 500 Da. The number of commercially available products based on transdermal or dermal delivery has been limited by these requirements. In recent years various passive and active strategies have emerged to optimize delivery. The passive approach entails the optimization of formulation or drug carrying vehicle to increase skin permeability.

However, passive methods do not greatly improve the permeation of drugs with molecular weights >500 Da. In contrast, active methods, normally involving physical or mechanical methods of enhancing delivery, have been shown to be generally superior. The delivery of drugs of differing lipophilicity and molecular weight, including proteins, peptides and oligonucleotides, has been shown to be improved by active methods such as iontophoresis, electroporation, mechanical perturbation and other energy-related techniques such as ultrasound and needle less injection. In the last 25 years numerous methods of overcoming the skin barrier have been described, but they can broadly be divided into two main categories defined as either passive or active method

Passive Methods for Enhancing

The conventional means of applying drugs to skin include the use of vehicles such as ointments, creams, gels and “passive” patch technology. 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. Such approaches include the use of penetration enhancers, supersaturated systems, prodrugs or metabolic approach, liposomes and other vesicles. However, the amount of drug that can be delivered using these methods is still limited since the barrier properties of the skin are not fundamentally changed³².

Patch System - Several technologies have been successfully developed to provide rate control over the release and transdermal permeation of drugs. These technologies can be classified into four main approaches as follows

1) Membrane Moderated System

In this system, the drug reservoir is totally encapsulated in a shallow compartment molded from a drug impermeable metallic- plastic laminate and a rate controlling polymeric membrane. The drug molecules are permitted to release only through the rate controlling polymeric membrane.

2) Adhesive Diffusion-Controlled System

In this system the drug reservoir is formulated by directly dispersing the in an adhesive polymer and then spreading the medicated adhesive, by solvent casting, onto a drug impermeable metallic plastic backing to form a thin drug reservoir layer.

3) Matrix Dispersion Type System

In this system, the drug reservoir is formed by homogeneously dispersing the drug solids in a hydrophilic or lipophilic polymer matrix and the medicated polymer is then molded into a medicated disc with a defined surface area and controlled

thickness. This reservoir containing polymer disc is then glued onto an occlusive base plate in compartment fabricated from a drug impermeable plastic backing.

4) Microreservoir System

In this system, the drug reservoir is formed by first suspending the drug solids in aqueous solution of water soluble polymer and then dispersing homogeneously the drug suspension in a lipophilic polymer, by high shear mechanical force, to form thousands of unreachable.

Permeation Enhancer

Among the myriad strategies employed to increase both the amount of a therapeutic agent traversing the skin and the range of drugs that can be effectively delivered through this route, lies in the application of chemical penetration enhancers. These agents interact with stratum corneum constituents to promote drug flux. Such materials have been used empirically in topical and transdermal preparations for as long as pastes, poultices, creams, and ointments have been applied to skin. Many chemicals have been evaluated for increasing permeant delivery through the stratum corneum but to be of clinical value the penetration enhancer must exert its effects without injuring underlying viable skin cells. In addition, accelerants should act reversibly, i.e., stratum corneum barrier properties should reduce only temporarily. Desirable properties for such an enhancer acting on human skin include the following

- It should be pharmacologically inert within the body, either locally or systemically.
- It should not irritate or induce allergic responses.
- The enhancer should work rapidly with a predictable onset of action.
- The operation of enhancement (both in terms of activity and duration of effect) should be predictable and reproducible.
- When the enhancer leaves the skin, the barrier resistance of the membrane should return rapidly and fully.
- The penetration enhancer should work unidirectional, i.e., should allow medicaments to enter the body while preventing the release of endogenous materials.
- The accelerant should be suitable for formulation into topical and transdermal preparations, being compatible with drugs and excipients and promoting appropriate drug solubility in the formulation.
- It should be cosmetically acceptable, being odorless, colorless, and with appropriate skin feel.

Furthermore, accelerants have also been combined with several other strategies for promoting drug delivery through skin, such as iontophoresis. For example, fatty acids have been used synergistically to enhance hormone delivery by iontophoresis. Iontophoresis has also been employed to increase amounts of promoters in the skin.

Likewise, chemicals have been employed with electroporation for two principal reasons

1. To obtain an additional enhancement effect alongside the creation of pores in the stratum corneum bilayers.
2. To stabilize and possibly expand the transient pores that the high-voltage pulses create.

Major Classes of Chemical Penetration Enhancers

Accelerants operate in complex, interacting ways to change the intercellular region of the horny layer by fluidization, alteration of polarity, phase separation, or lipid extraction. More drastically, they may form vacuoles within corneocytes, denature their keratin or splits quames. The following selection of enhancers illustrates examples of all these modes of action.

Sulfoxides and Similar Chemicals

Dimethylsulfoxide (DMSO), the archetypal penetration enhancer, is a powerful aprotic solvent that is colorless, odorless, and hygroscopic; its value as an enhancer may be predicted from its use chemically as a universal solvent. Extensive investigations on the accelerator activities of DMSO show it to be effective in promoting the flux of both lipophilic and hydrophilic permeants, e.g., antiviral agents, steroids, and antibiotics.

Azone

Azone (1-dodecylazacycloheptan-2-one or laurocapram), the most famous modern enhancer, was the first accelerant specifically designed. It is a hybrid of a cyclamide, as with pyrrolidone structures, with an alkyl sulfoxide; the sulfoxide group presumed to provide some of the disadvantages of DMSO is absent. Azone is a colorless, odorless liquid possessing a smooth, oily but yet no greasy feel. It is highly lipophilic with a log P octanol=water around 6.2 and is soluble in, and compatible with, most organic solvents, including propylene glycol (PG) and alcohols. Azone increases the permeation of many drugs such as steroids, antibiotics, and antiviral agents. Reports describe its activity in promoting the flux of both hydrophilic and lipophilic medicaments. The efficacy of Azone appears to be strongly concentration dependent and is also influenced by the choice of vehicle in which it is applied. Azone is most effective at low concentrations, typically between 0.1% and 5%, often between 1% and 3%.

Pyrrolidones

A range of pyrrolidones and structurally related compounds has been investigated as potential penetration enhancers in human skin. As with azone and many other accelerants, they apparently have greater effects on hydrophilic diffusants than for lipophilic permeants, although this may be attributable to the greater enhancement potential for the poor hydrophilic permeants. N-methyl-2-pyrrolidone (NMP) and 2-pyrrolidone (2P) are the most widely studied enhancers of this group

Fatty acids

A wide variety of long-chain fatty acids increase transdermal delivery; the most popular is oleic acid.

Alcohols, Fatty alcohols and Glycols

Ethanol is used in many transdermal formulations and is often the solvent of choice for incorporation into patches. As with water, ethanol permeates rapidly through human skin with a steady-state flux of approximately 1 mg/cm²/h. Ethanol exerts its accelerant activity through various mechanisms. Firstly, as a solvent, it can increase the solubility of the drug in the vehicle—although at steady state the flux of a permeant from any saturated, non enhancing, vehicle should ideally be equivalent.

Surfactants

As with some of the materials described previously, surfactants are incorporated into many therapeutic, cosmetic, and agrochemical preparations. Usually, they are added to formulations to stabilize emulsions and suspensions or to solubilize lipophilic active ingredients, and so they have the potential to dissolve lipids within the stratum corneum. Typically composed of lipophilic alkyl or aryl fatty chains, together with a hydrophilic head group, surfactants are often described in terms of the nature of the hydrophilic moiety. Anionic surfactants include sodium lauryl sulfate (SLS), cationic surfactants encompass cetyltrimethyl ammonium bromide, the nonoxynol surfactants are nonionic surfactants and zwitterionic surfactants include dodecyl betaine.

Essential oils, Terpenes and Terpenoids

Terpenes, found in essential oils, are nonaromatic compounds comprising only carbon, hydrogen, and oxygen. Several terpenes have long been used as medicines, flavorings, and fragrance agents. For example, menthol is traditionally employed for inhalation and has a mild antipruritic effect when incorporated into emollient preparations. It is also used as a fragrance and to flavor toothpastes, peppermint sweets, and mentholated cigarettes. The data yielded some structure–activity relationships in that hydrocarbon terpenes were less potent accelerants for this hydrophilic drug than were

alcohol- or ketone-containing terpenes, and the greatest enhancement activity was shown by the oxide terpenes and terpenoids.

Phospholipids

Many studies have employed phospholipids as liposomes (vesicles) to transport drugs into and through human skin. Phospholipids can occlude somewhat the skin surface and thus can increase tissue hydration, which can increase drug permeation. When applied to the stratum corneum as vesicles, phospholipids can sometimes fuse with stratum corneum lipids. This collapse of structure liberates permeant into the vehicle in which the drug may be poorly soluble and hence thermodynamic activity temporarily increases, facilitating drug delivery.

Ceramide Analogs

An interesting novel approach in penetration enhancer science was to synthesize and test a series of ceramide analogs containing eight polar groups and six chain lengths based on L-serine and glycine (ceramides form the main components of the intercellular lipid domains).

Vesicular Carriers for Enhanced Delivery through the Skin

Dermal and transdermal delivery requires efficient penetration of compounds through the skin barrier, the bilayer domains of intercellular lipid matrices, and keratin bundles in the stratum corneum (SC). Lipid vesicular systems are a recognized mode of enhanced delivery of drugs into and through the skin. However, it is noteworthy that not every lipid vesicular system has the adequate characteristics to enhance skin membrane permeation. Specially designed lipid vesicles in contrast to classic liposomal compositions could achieve this goal³⁴.

Liposomes—Phospholipid Vesicles For Topical Administration Of Drugs

Mezei and Gulusekharan first proposed liposomes for drug topical administration to the skin more than 25 years ago. The basic components of liposomes are phospholipids (phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, dipalmitoyl phosphatidylcholine, and others), cholesterol, and water. Liposomes may vary significantly in terms of size (from tens of nm to microns) and structure. In liposomes, one or more concentric bilayers surround an aqueous core generating small or large unilamellar vesicles (SUV, LUV) or multilamellar vesicles (MLV), respectively. Liposomes for topical delivery are prepared by the same classic methods widely described in the literature for preparation of these vesicles. The majority of the liposome preparation methods are complicated multistep processes. These methods include hydration of a dry lipid film, emulsification, reverse phase

evaporation, freeze-thaw processes, and solvent injection. Liposome preparation is followed by homogenization and separation of untrapped drug by centrifugation, gel filtration, or dialysis. These techniques suffer from one or more drawbacks such as the use of solvents (sometimes pharmaceutically unacceptable), an additional sizing process to control the size distribution of final products (sonication, extrusion), multiple-step entrapment procedure for preparing drug-containing liposomes, and the need for special equipment. The stability of liposomes is of great concern during the design of topical formulations. As liposomal preparations contain an aqueous phase, the lipid vesicles may be subject to a series of adverse effects including aggregation, fusion, phospholipid oxidation, and hydrolysis.

Niosomes-Nonionic Surfactant Vesicle

Nonionic surfactant vesicles (niosomes) were first proposed by Handjani-Vila et al. as systems to improve accumulation of the active molecule within the skin and thus benefit cosmetic products. Niosomes are bilayer structures formed from amphiphiles in aqueous media. Many types of surfactants have been used for formulation of niosomes. Basically, these vesicles are analogous to liposomes. Niosome formation requires the presence of a particular class of amphiphile and aqueous solvent. Among the surfactants we can enumerate polyoxyethylene alkyl ethers, sorbitan esters, polysorbate-cholesterol mixtures, crown ether derivatives, per-fluoroalkyl surfactants, alkyl glycerol ethers, and others. The hydrophobic moiety of the surfactant may contain one or more alkyl (C₁₂-C₁₈) or perfluoroalkyl (C₁₀) groups or a steroid group. Among the hydrophilic headgroups found in these amphiphiles are ethylene oxides, glycerols, crown ether, polyhydroxyls, and sugars. The hydrophilic and the hydrophobic moieties are generally linked by ether, ester, or amide bonds. The methods for preparation of niosomes are similar and as complicated as those used for liposomes. One of the most frequently utilized techniques consists of the hydration of a mixture of the surfactant-lipid at elevated temperature followed by optional size reduction (by sonication, extrusion, homogenization, etc.) to obtain a homogeneous colloidal dispersion and separation of the untrapped drug.

Ethosomes

Although frequently referred to as a kind of liposomes, ethosomes are very different from other lipid vesicles by their composition, structure, mechanism of action, and delivery properties. Ethosomal carriers contain soft lipid vesicles (mainly composed of phospholipids, ethanol, and water) in a hydroethanolic milieu. They have appropriate

features, designed to allow for enhanced delivery by passive transport to the deep skin³⁵.

Transfersomes-Ultradeformable Liposomes

Cev and his co-workers first developed the concept of transfersome as a recent tool for effective transdermal drug delivery in 1992³⁶. Transfersomes are basically modified liposome developed to increase transdermal permeation of drug. These vesicular transfersomes are several orders of magnitude more deformable than standard liposome and thus well studied for skin penetration. Deformability of skin penetration is achieved by using surface-active agent by appropriate ratio. Transfersomes are complex, most often vesicular, aggregates optimized to attain extremely flexible and self-regulating membrane, which makes vesicle very deformable³⁷. Transfersomes possess higher entrapment efficiency, which protects the encapsulated drug from degradation. Transfersomes act as a depot releasing their contents slowly. They are more stable and have high penetration due to deformity of vesicular membrane by which they can pass through the narrow constriction; and this deformity of vesicular membrane is responsible for better skin penetration, resulting in a higher transdermal flux encapsulated drug³⁸.

Mechanism of penetration

The passage of transfersomes across the skin is a function of vesicles membrane flexibility, hydrophilicity and ability of the vesicle for retaining integrity. When transfersome vesicles in suspension form are applied on the skin surface, water gets evaporated from the skin surface and the vesicles began to dry out due to strong polarity of transfersomes ingredient vesicles get attracted toward area of higher water content in the narrow gaps between adjoining cells in the skin. This process along with the vesicles membrane deformability enables transfersomes aggregates to open the tiny pores temporarily through which water normally gets evaporated between the cells. Such newly activated intercellular channels can accommodate sufficiently deformable vesicles, maintaining their integrity and changing their shape to fit the channel reach region of high water content in the deeper skin layers in which the vesicles get distributed between the cells³⁹. Subheet Jainet et al , Rachna Sapre et al , Ashok K.Tiware et al, and Narendra K Jain et al investigate transfersome gel formulations of levonorgesterol for transdermal drug delivery. Protransfersome gel (PTG) formulations of levonorgestrel were prepared and characterized for vesicle shape, size, entrapment efficiency, turbidity, and drug permeation across rat skin and were evaluated for their stability. The system was evaluated in vivo for

biological assay of progestational activity including endometrial assay, inhibition of the formation of corporalutea, and weight gain of uterus. The effects of different formulation variables (type of alcohol, type and concentration of surfactant) on transdermal permeability profile were investigated⁴⁰. Tian-Zhi-YANG et al investigate the possibility of enhancing effect of deformable vesicle on buccal delivery of insulin, two kinds of vesicles with and without presence of Sodium deoxycholate (deformable vesicles and conventional vesicles) were prepared by reverse phase evaporation methods⁴¹.

Active Methods for Enhancing Transdermal Drug Delivery⁴²

- Iontophoresis
- Electro osmosis
- Ultrasound (Sonophoresis and Phonophoresis)
- Laser Radiation and Photomechanical Waves
- Radio Frequency
- Magnetophoresis
- Electroporation
- Micro needle-Based Devices
- Needle less Injection

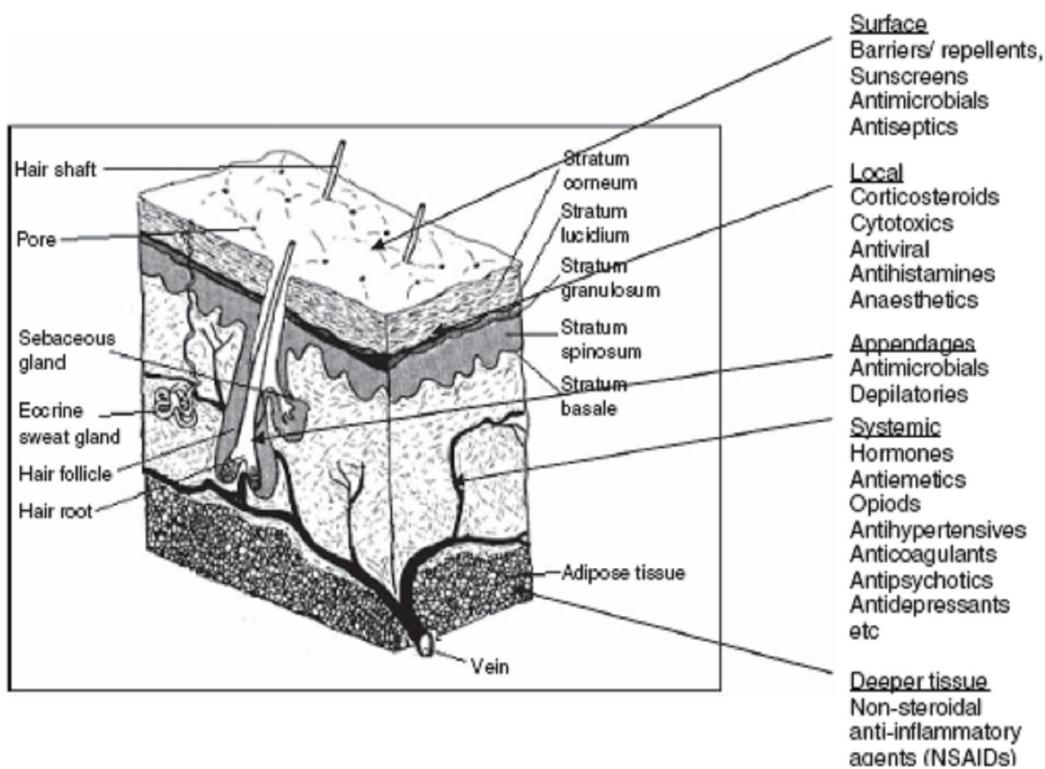


Fig. 1: The typical structure of mammalian skin

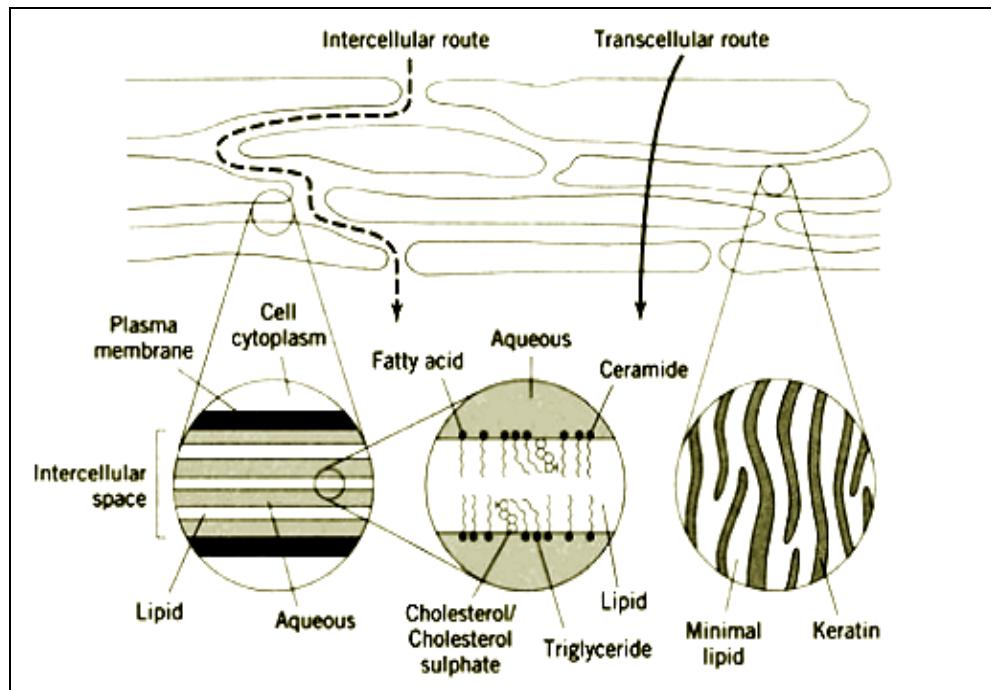


Fig. 2: Possible micro routes of drug permeation through human skin intercellular or transcellular pathway

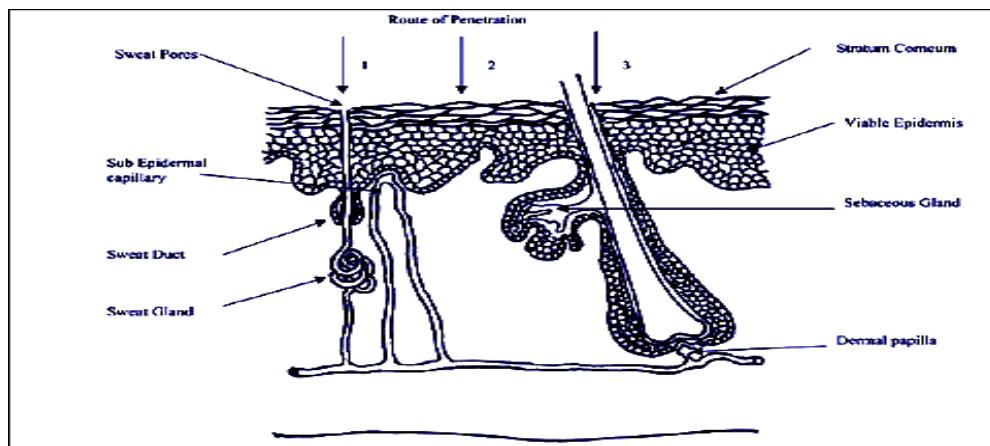


Fig. 3: Simplified representation of skin showing routes of penetration:

- 1 Through the sweat ducts.
- 2 Directly across the stratum corneum.
- 3 via the hair follicles²⁴

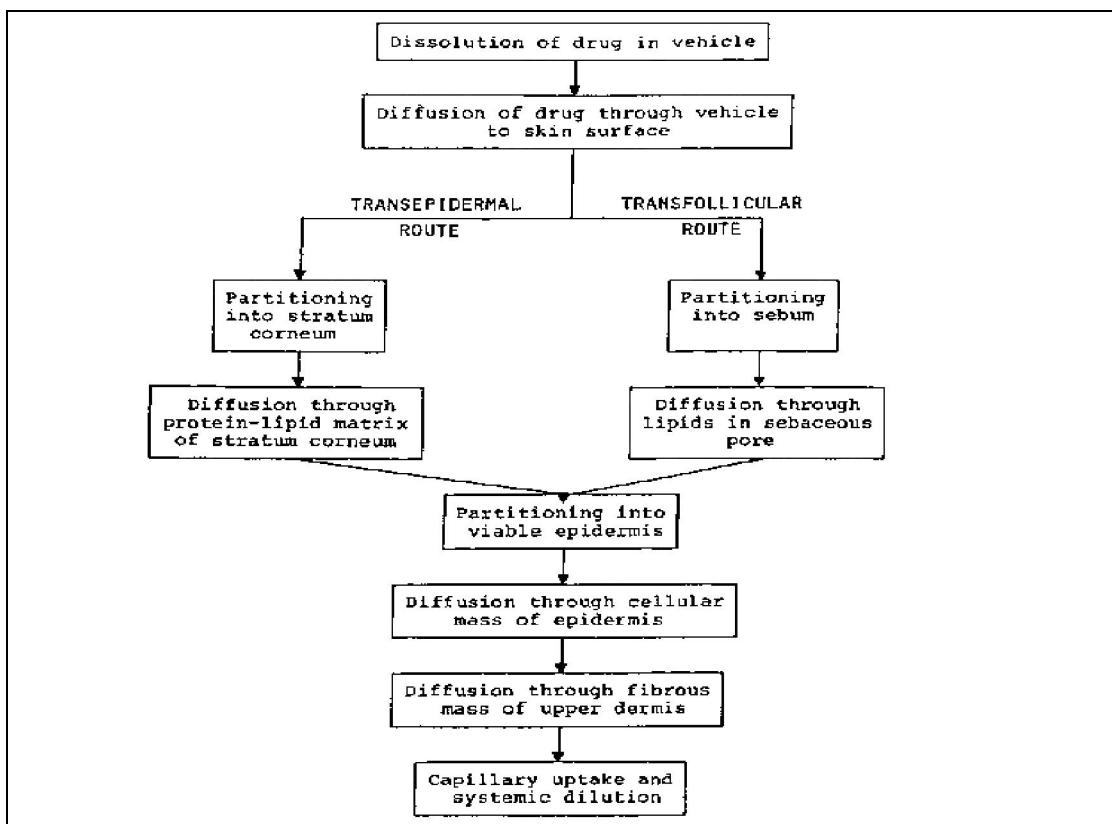


Fig. 4: Percutaneous Absorption Process³¹

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