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SKIN PENETRATION ENHANCEMENT IN NOVEL DRUG DELIVERY SYSTEM

Nazneen Ansari[1], Ravi Bharti[1], N. Syed Abdul Kader[1], Naresh Mandavi[1], Shekhar Verma[1], Chanchal Deep Kaur[2], Gyanesh Kumar Sahu[3] and Harish Sharma[1]*

[1]Shri Shankaracharya Technical Campus, Shri Shankaracharya Group of Institutions, Faculty of Pharmaceutical Sciences, Bhilai, Chhattisgarh, India.

[2]Shri Rawatpura Institute of Pharmacy, Kumhari, Durg, Chhattisgarh.

[3]Rungta College of Pharmaceutical Sciences and Research, Bhilai.

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***Corresponding Author**
Harish Sharma
Shri Shankaracharya Technical Campus, Shri Shankaracharya Group of Institutions, Faculty of Pharmaceutical Sciences, Bhilai, Chhattisgarh, India.

ABSTRACT

The skin provides an effective barrier to protect the body from the penetration of molecules and micro-organisms in the external environment, and from excessive loss of water to maintain homeostasis. The main skin barrier resides in the stratum corneum due to its exclusive structure of layers of flattened corneocytes surrounded by lipid bilayers composed largely of ceramides. In recent years, the focus of pharmaceutical research is progressively shifting to the development of drug delivery systems rather than finding newer chemical entities for an all-round improvement in drug therapy. Multiferous materials and principles have been employed to generate a wide variety of carrier classes such as polymer-based particulate systems (microspheres, microcapsules, nanoparticles, and transdermal patches) and rigid, semi-rigid and vesicular lipoidal colloid drug delivery carriers (liposomes, niosomes, microemulsions, micelles). Novel drug delivery systems (NDDS) are particulate or vesicular dosage form in nanometer size range. NDDS are essentially required for effective transportation of loaded drug across the skin barriers. Nanotechnology defined as a tiny science. Design, characterization, production, categorization, and applications of structures, devices and systems by controlling shape and size at nanometer scale is refers to nanotechnology. From nanotechnology we can achieve better therapeutic action, enhanced bioavailability and better patient compliance. The present review focuses on the advantages of techniques which improves therapeutic efficacy through enhanced retention of nanocarrier.

KEYWORDS: Skin Permeations, Novel Drug Delivery System (NDDS), Nanoparticles, Startum Corneum (SC), Skin Barriers.

INTRODUCTION

Novel drug delivery systems are designed to achieve a continuous delivery of drugs at predictable and reproducible kinetics over an extended period of time in the circulation. The potential advantages of this concept include minimization of drug related side effects due to controlled therapeutic blood levels instead of oscillating blood levels, improved patient compliance due to reduced frequency of dosing and the reduction of the total dose of drug administered.[1,2] The method by which a drug is delivered can have a significant effect on its efficacy. Some drugs have an optimum concentration range within which maximum benefit is derived, and concentrations above or below this range can be toxic or produce no therapeutic benefit at all. On the other hand, the very slow progress in the efficacy of the treatment of severe diseases, has suggested a growing need for a multidisciplinary approach to the delivery of therapeutics to targets in tissues.[3]

CARRIERS USED IN NOVEL DRUG DELIVERY SYSTEM

The novel drug delivery systems also have the advantage of penetrating more efficiently into the circulation than do non particulate systems, such as conventional formulations, so long as the size is selected in an appropriate manner. This provides a high local concentration over a prolonged period.[4,5,6] The drug-loaded vesicular and particulate delivery systems (liposomes, polymeric microspheres, and solid lipid nanoparticles) for topical treatment are advantageous compared to conventional available topical delivery system. The novel carrier systems that are under investigation for application and treatment of acne include liposome, niosome, microsponge, microemulsion, microsphere, SLN, hydrogel, aerosol, fullerenes and so forth. It is given in figure-1.[7,8]

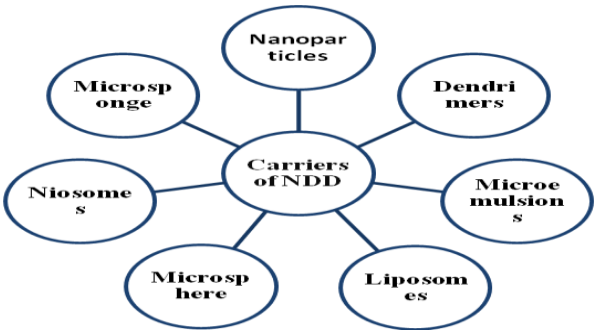

Figure-1: Different Carrier Systems of NDDS.

HUMAN SKIN

The skin provides the largest interface between the human body and the external environment. Therefore, one of its most important functions is to regulate what enters the body via the skin, as well as what exits. In general, the skin is designed to let very little enter, since other tissues, such as the permeable epithelia of the gastrointestinal tract and lung, provide the primary means of regulated entry into the body.[9] The skin ' s remarkable barrier properties are due in large part to the stratum corneum, which represents the thin outer layer of the epidermis. In contrast to other tissues in the body, the stratum corneum consists of corneocytes (composed primarily of aggregated keratin fi laments encased in a cornified envelope) that are surrounded by an extracellular milieu of lipids organized as multiple lamellar bilayers. These structured lipids prevent excessive loss of water from the body and likewise block entry of most topically applied drugs, other than those that are lipid-soluble and of low molecular weight. This poses a significant challenge to administering medications via the skin either for local cutaneous effects or as systemic therapy following their entry into superficial dermal capillaries.[10]The skin is the largest organ of the body weighing more than 10 % of the total body mass. Forming the outermost layer of the human body, it has two important functions, namely communication and protection.[9]

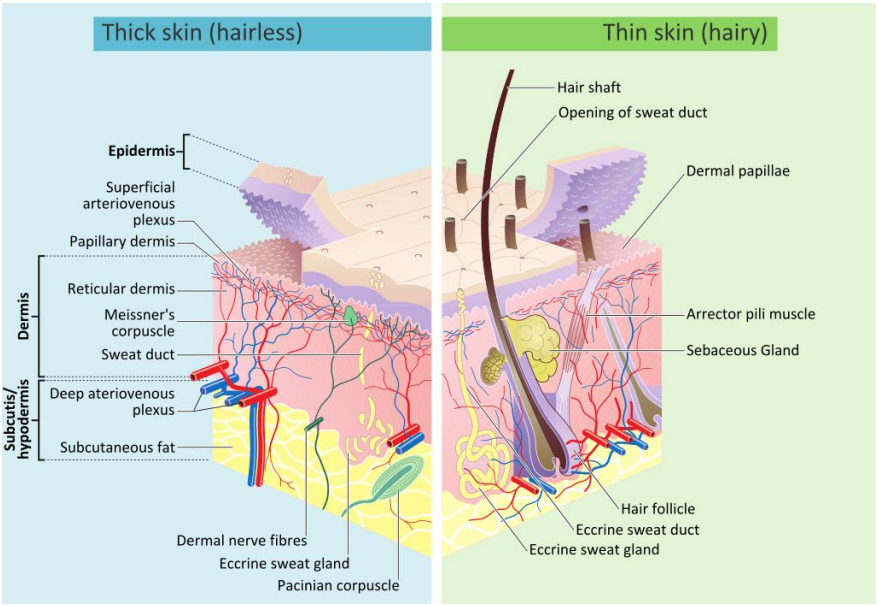

Figure 2- Structure of human skin layers.[55]

STRUCTURE OF HUMAN SKIN

The structure of skin is depicted in (Figure-2). The skin is basically composed of two layers (epidermis and dermis) with an adjacent subcutaneous fat tissue. The epidermis forms the

outer layer of the body comprising non-viable (stratum corneum) and viable cell layers. The epidermis is generated in the undulating basal cell layer at the epidermal dermal junction.[11] On their way to the skin surface the keratinocytes start to differentiate and undergo a number of changes in both structure and composition during migration through the stratum spinosum and stratum granulosum. The final differentiation occurs in the stratum corneum.[12] The stratum corneum forms the major barrier for substances to permeate across the epidermis. The stratum corneum consists of dead keratinocytes coated with an impermeable proteinous cornified envelope. The corneocytes are surrounded by lipid matrix.[12] This lipid matrix is arranged in multiple layers forming lipid lamellae.[13] Due to the impermeable cornified envelope the intercellular lipid matrix forms the main rather tortuous pathway for permeation of substances across the stratum corneum. The dermis is located beneath the epidermis. The thin upper dermis, which is in direct contact with the undulating epidermis, is the papillary dermis while the thicker main part of the dermis is called reticular dermis. It is a fibrous, flamentous and amorphous connective tissue consisting of collagen, elastin, ground substance and fibroblasts.[14,15,16] Its main function is to provide support for the epidermis and embedded structures (blood vessels, nerves, hair follicles, sweat and sebaceous glands) as well as elasticity of the skin.[10] In contrast to the epidermis, this tissue is highly vascularised. The subcutaneous fat tissue is underlying the dermis. It is an assembly of fat cells linked by collagen fibres thereby creating a thermal barrier, energy storage and mechanical cushion for the body.[10,17]

Appendages

Appendages are skin structures penetrating the skin and originate either from the dermis or the subcutaneous fat. Their presence varies in different skin regions of the body. Since they emerge from the skin, the appendages form discontinuities in the stratum corneum and can therefore act as potential sites of formulation accumulation and routes of penetration.[10,17]

Sweat gland

Apocrine and eccrine glands are present in large numbers and distributed over the entire body. Apocrine glands emerge into the follicular duct and are located in the axilla and perianal region in adults. Therefore it has been proposed, that the apocrine glands do not contribute to the thermoregulatory function of the sweat glands but are remnants of the secondary sexual organs.[17] Eccrine sweat glands are smaller than the apocrine glands and are spread over the whole body surface except from mucosal tissue. They excrete sweat

(hypotonic water) via the sweat duct to the skin surface. These sweat ducts perturb the stratum corneum in a spiral form and straighten in deeper skin layers. The secretory gland itself is coiled and situated in the lower dermis. Their main function is the thermal regulation of the body.[10]

Pilosebaceous unit

The pilosebaceous unit consists of the hair follicle and the sebaceous gland. The hair follicle can be divided into two classes. The smaller vellus hair is rather thin and reaches down into the dermis. The larger terminal hair extends down into the subcutaneous fat.[18] The terminal hair occurs mainly in the scalpskin which is the region with the highest density of hair follicles. Sebaceous glands are located at the whole body surface, however, their density and activity depends on age and sex.[19,20,21] A high density of sebaceous glands is present in scalp and forehead skin, while in palm and sole the sebaceous glands are absent.[22] Sebum, mainly consisting of triglycerides, free fatty acids, squalene and waxes, is secreted by the sebaceous gland into the hair duct at a depth of about 500 µm.[23,24.25,26] This sebum protects the body from microbial infection and prevents water loss from the body.[26]

The hair follicle

The basic structure of the hair follicle is displayed in. The hair follicle can be divided into several sections starting from the skin surface. The infundibulum is the upper part of the hair follicle up to the sebaceous duct. In this area, no tight connection between the hair shaft and the skin is present. Therefore, the hair shaft can move freely within the skin. This gap is filled with sebum of the sebaceous gland. The thickness of the stratum corneum decreases deeper in the infundibulum. This thinned stratum corneum provides a weaker barrier for penetration compared to the stratum corneum at the skin surface.[27] The isthmus is located just below the sebaceous duct and up to the area where the arectorpili muscle is attached to the hair follicle. From the isthmus upward the hair follicle is permanent and does not disintegrate during the growth of the hair follicle. However in this region the inner root sheet is disintegrating and disappears between the outer root sheet and the cuticle further to the surface. The bulge area is located where the arectorpili muscle is in contact with the hair follicle. This area is important for regulatory processes during hair growth.[28] Below the bulge area starts the lower follicle with the keratogeneous zone. The lowest part of the hair follicle is the hair bulb, where the matrix cells, the basement membrane and the follicular papilla are located. These structures are key features in the regulation of the hair growth.[29]

Stratum Corneum

The figure is depicted in (figure-3). The stratum corneum is a composite material made of proteins and lipids structurally organized as " bricks and mortar " Instead of being uniformly dispersed, the highly hydrophobic lipids in normal stratum corneum are sequestered within the extracellular spaces, where this lipid-enriched matrix is organized into lamellar membranes that surround the corneocytes.[30] Hence, rather than stratum corneum thickness, variations in number of lamellar membranes (=lipid weight %), membrane structure, and/or lipid composition provide the structural and biochemical basis for site-related variations in permeability.[31] It follows, then, that the extracellular, lipid-enriched matrix of the stratum corneum comprises not only the structure that limits transdermal delivery of hydrophilic drugs, but also the so-called stratum corneum" reservoir "[32],within which lipid soluble drugs, such as topical corticosteroids, can accumulate and be slowly released. The layers of skin are epidermis, dermis, hypodermis.

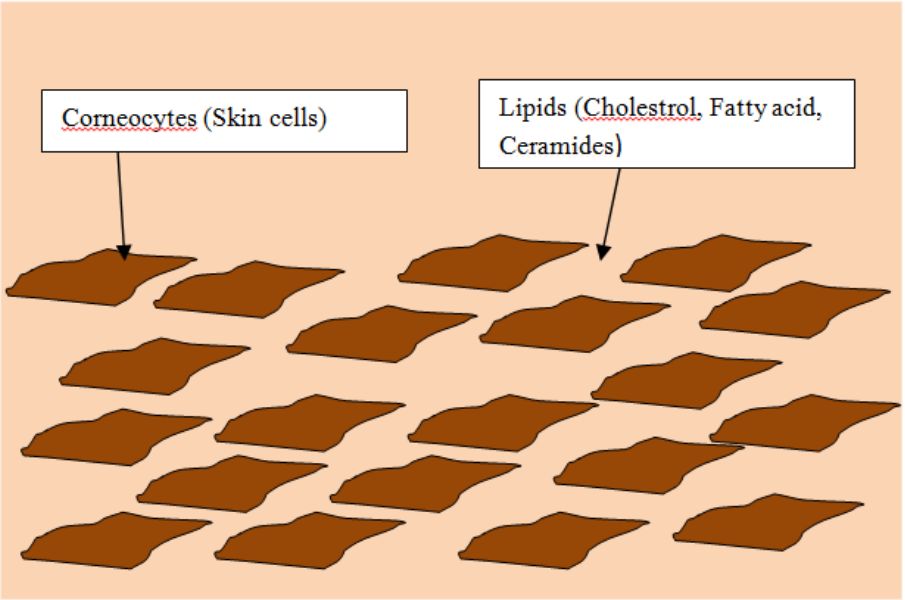

Figure-3: Structure of Stratum Corneum.

SKIN BARRIER

TYPES OF SKIN BARRIERS

A. Biosynthetic activities

Epidermal differentiation is a vectorial process that is accompanied by dramatic changes in lipid composition, including loss of phospholipids with the emergence of ceramides, cholesterol and free fatty acids in the stratum corneum.[33,34] Although epidermal lipid synthesis is both highly active and largely autonomous from systemic influences, it can be regulated by external influences, i.e. changes in the status of the permeability barrier.[35] Acute perturbations of the permeability barrier stimulate a characteristic recovery sequence that leads to restoration of normal function over about 72 hours in young skin (the cutaneous stress test). This sequence includes an increase in cholesterol, free fatty acid and ceramide synthesis that is restricted to the underlying epidermis, and attributable to a prior increase in mRNA and enzyme activity/mass for each of the key synthetic enzymes. Furthermore, synthesis of each of the three key lipids is required for normal barrier homeostasis, i.e. topically applied inhibitors of the key enzymes in each pathway produce abnormalities in permeability barrier homeostasis.[35]

B. Lamellar body secretion

The unique two-compartment organization of the stratum corneumis attributable to the secretion of lamellar body-derived lipids and co-localized hydrolases at the stratum granulosum – stratum corneum interface.[30] Under basal conditions, lamellar body secretion is slow, but sufficient to provide for barrier integrity. Following acute barrier disruption, calcium is lost from the outer epidermis, and much of the preformed pool of lamellar bodies in the outermost cells of the stratum granulosum is quickly secreted. Calcium is an important regulator of lamellar body secretion, with the high levels of Ca 2 + in the stratum granulosum restricting lamellar body secretion to low, maintenance levels.[36]

C. Extracellular processing

Extrusion of the polar lipid contents of lamellar bodies at the stratum granulosum – stratum corneum interface is followed by the processing of those lipids into more hydrophobic species that form mature, lamellar membranes.[37] The extracellular processing of glucosylceramides, phospholipids and cholesterol sulfate with accumulation of ceramides, free fatty acids and cholesterol in the stratum corneum is attributable to the co-secretion of a set of hydrolytic enzymes.[30] Extracellular processing of *glucosylceramides* plays a key role in barrier homeostasis.[37] In addition, phospholipid hydrolysis, catalyzed by one or more secretory phospholipases (e.g. sPLA 2), generates a family of non-essential free fatty acids, which are required for barrier homeostasis.[38,39,40] Since applications of either

bromphenacylbromide or MJ33 (chemically unrelated sPLA2 inhibitors) modulate barrier function in intact skin, sPLA 2 appears to play a critical role in barrier homeostasis. Moreover[38,39,40], applications of either inhibitor to perturbed skin sites delay barrier recovery.

D. Acidification

The fact that the stratum corneum displays an acidic external pH ("acid mantle") is well documented, but its origin is not fully understood. Extra epidermal mechanisms (including surface deposits of eccrine- and sebaceous gland-derived products as well as metabolites of microbial metabolism), endogenous catabolic processes (e.g. phospholipid-to-free fatty acid hydrolysis, deamination of histidine to urocanic acid; and local generation of protons within the lower stratum corneum (by sodium-proton antiporters [NHE 1] inserted into the plasma membrane,[41,42] could actively acidify the extracellular space. These mechanisms would explain not only the pH gradient across the interstices of the stratum corneum, but also selective acidification of membrane microdomains within the lower stratum corneum. The concept that acidification is required for permeability barrier homeostasis is supported by the observation that barrier recovery is delayed when acutely perturbed skin sites are immersed in neutral pH buffers,[43] or when either the sodium – proton exchanger/antiporter or sPLA 2 - mediated phospholipid catabolism to free fatty acids is blocked.[41] Acidification appears to impact barrier homeostasis through regulation of enzymes involved in extracellular processing, such as β -glucocerebrosidase and acidic sphingomyelinase, which exhibit acidic pH optima.[43]

DRUG PERMEATION THROUGH THE SKIN

The skin is a selectively permeable barrier. As such, different drugs permeate through the skin at different rates. The rate of drug permeation is expressed as the flux (*J*),i.e. the amount of drug permeated per unit area, per unit time (usually µg/cm/h). The flux is determined by(a) the permeability of the skin to the permeant and (b)the concentration gradient (_*C*) of the permeant across the skin (usually µg/ml), according to

Eq. 1: *J* = *K*p-*C*

In Eq. 1,skin permeability is defined by the permeability coefficient, *K*p (usually cm/h). Assuming passive drug absorption, the permeability coefficient is a combined measure of the partition coefficient (*P*, which depict show readily the permeant partitions from the

formulation into the skin), the diffusion coefficient (*D*, which measures how readily the permeant diffuses through the skin) and the diffusional path length (*h*), according to

Eq. 2: *K*p =*P* -*D H*

The processes of partitioning and diffusion (and thus skin permeability, according to Eq. 2) are highly dependent on the physicochemical properties of the permeant, such as molecular mass and hydrophilicity. As a general rule, molecules that permeate the skin most readily have a molecular mass of <500 Da and are moderately hydrophilic, with an octanol-water partition coefficient (log *P* octanol–water) of 1–3. The quantitative relationship between skin permeability (defined by *K*p), molecular mass(MW) and hydrophilicity (defined by log *P* octanol–water) is widely described using (Potts RO, Guy R H, et al, 1992) Eq.3: log*K*p = 0.71 _ log *P* octanol-water 0.0061 MW 2.74. Other factors that may influence skin permeation include hydrogen bond activity, molecular volume, melting point and solubility. Other mathematical models have been devised to relate the role of these parameters to skin permeation.[44,45]

PERMEATION PATHWAYS

This is depicted in (figure-4). A molecule can permeate through the skin via either the trans epidermal pathway (diffusing across the skin layers) or the appendageal pathway through hair follicles or sweat ducts. The combined flux of these two pathways determines the overall observed flux across the skin.

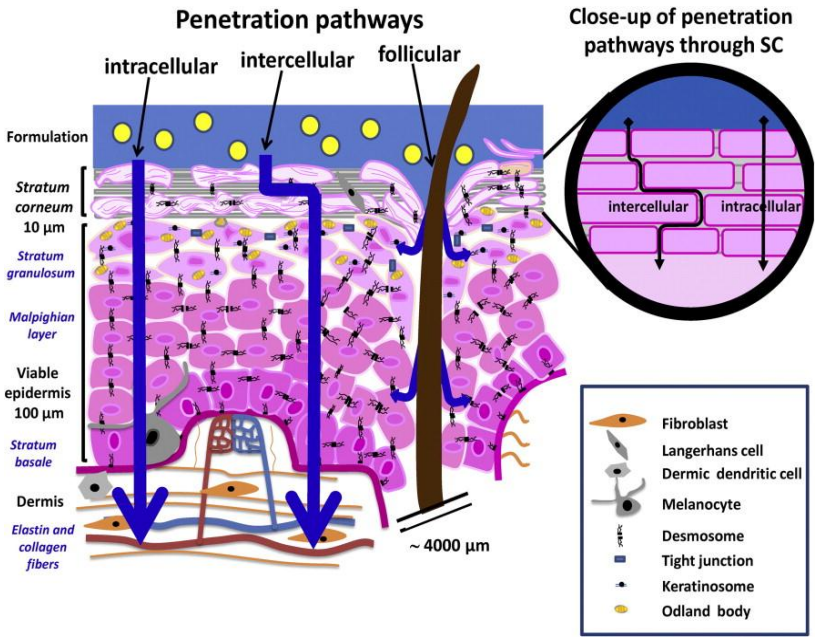

Figure-4: Skin Permeation Pathways.[46]

A. Transepidermal Pathway

In the transepidermal pathway, the permeant traverses the intracellular and/or extracellular spaces, from the epidermis to the dermis and hypodermis. The molecule may do so either transcellularly or inter-cellularly. The transcellular route requires that the permeant traverse the alternating layers of cells and extracellular matrix. This involves a sequence of partitioning and diffusion into alternating hydrophilic and lipophilic domains. The cells and substances that comprise the hydrophilic or lipophilic domains vary between skin layers, but generally the interiors of cells are more hydrophilic than the extracellular rmatrix. In the intercellular route, the permeant navigates the tortuous path within the extracellular matrix, without traversing the cells. Small hydrophilic molecules generally favour the transcellular route over the intercellular route and vice versa for lipophilic molecules.

B. Appendageal Pathway

The appendageal (or shunt) pathway encompasses permeation through hair follicles (the transfollicular route) or sweat ducts. The transfollicular route has gained significant research interest in recent years. When considering polar and nonpolar pathways for penetration, it is usually assumed that polar compounds will penetrate through polar routes, while non-polar compounds will favor lipophilic routes.[56,57]

C. Intercellular pathway

Penetration between SC corneocytes is the pathway by which most compounds penetrate the skin. Since corneocytes are not stacked parallel to one another in the layers, when penetrating between them, a compound has a sinuous way to pass. This pathway is considered to enable free volume diffusion through lipid bilayers present between the cells. Most skin penetration enhancers were found to affect the intercellular lipid bilayers of which this route consists. Skin penetration accelerators such as dimethylsulphoxide (DMSO), laurocapram (Azone), glycols and surfactants enhance penetration into the skin by reversibly decreasing the diffusional resistance of its intercellular lipid bilayers.[47] These enhancers may not only act as solvents that solubilize the intercellular lipids but can also affect intercellular desmosomal connections or interfere with metabolic activity necessary for creation of an intact barrier. In normal skin conditions the effect on lipid bilayer structure is reversible. The decrease in the lipid bilayers' resistance to penetration can be due to a thermodynamic effect of fluidization

(decrease in lipid's transition temperature) or due to phase separation of lipids in the intercellular spaces.[58]

D. Intrafollicular pathway

The amount of sebaceous glands on the total skin surface represents not more than0.1%. Therefore there are scientists who believe that this route is not a significant penetration pathway for most molecules. Others claim that the appendages can bypass the low diffusivity of the SC and may act as diffusional shunts. When the follicle is the site of action, such as in acne, scientists find ways to target a compound to this site, by developing delivery systems with specific physic chemical properties.[48] It is believed to be hydrophilic in nature. It is composed of aqueous regions surrounded by polar lipids that create the walls of micro channels. It is known to have a high penetration resistance to lipophilic compounds but low resistance to hydrophilic compounds. It is also thought to be the route by which water evaporates through the skin. The localization of the hydrophilic pores is unclear. While some scientists claim compounds permeating through this route will penetrate between the corneocytes clusters through imperfections that create openings comprising of water, others think the intracellular keratin provides this pathway.[49] It may be that both pathways exist and that the preferred route for penetration is a function of molecular properties and the test model used. Supporting the first theory, a study conducted on the percutaneous penetration of baclofen through cadaver skin suggested that the polar pathway is intercellular and is made up of aqueous regions surrounded by polar lipids.[50]

TECHNIQUES OF ENHANCEMENT OF SKIN PERMEATION

Various technologies have been developed to bypass or modulate the barrier function of the skin and to allow easier passage of drugs into the dermal microcirculation; these can be categorized into physical and chemical approaches.[51] Different Penetration Enhancers have different mechanism of action. The miscibility and solution properties of enhancers can be responsible for enhanced transdermal delivery of water soluble drugs. Mechanisms for penetration enhancement of oil soluble drugs are due to partial leaching of epidermal lipids by this improvement of drug permeation through skin. To increase penetration of lipophilic compounds for this necessary to modify partitioning characteristics at the stratum corneum viable tissue interface. This may be possible by combining a penetration enhancer with a co-solvent. Some enhancers cause keratin to swell and leach out essential structural material from the stratum corneum thus reducing the diffusional resistance and increasing the permeability.[52,53]

The penetration enhancers can be classified into following groups (Figure-5)[54]

- Physical Enhancers
- Chemical Enhancers
- Natural Enhancers
- Misellaneous Enhancers

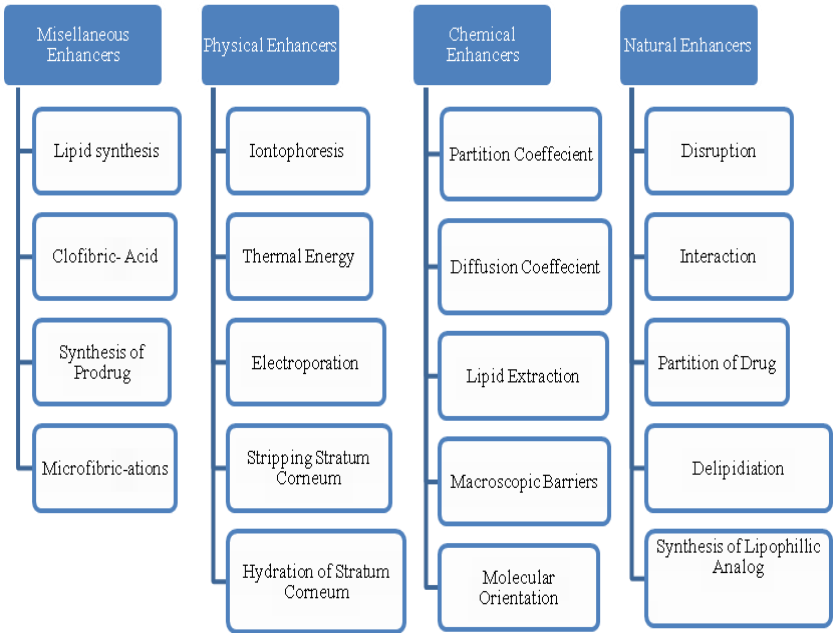

Figure 5: Skin Permeation Enhancers.

Table 1. Marketed preprations of skin permeation enhancers.

Brand Name	Company Name	Enhancement Method	Drug
E-Trans Sono Prep	Alza Corporation	Iontophoresis	Fentanly, Peptides
Powder Ject	Powder Ject Pharmaceutical Pvt Ltd	Needless Injector	Insulin
Med- Tat	Lipper-Man Ltd	Medicated Tattoos	Acetaminophen, Vitamin-C
Macroflux	Alza Corporation	Microprojection	Vaccine, Protein
CHADD	Zars, Inc	Thermal Energy	Idocaine, Tetracaine
SonoDerm	Imarx	Ultrasound	Large Molecule (Insulin)
Transdermal Assisted Delivery	Laser Norwood Abbey	Laser Radiation	Wide Range of Durg

Table 2. Cited patents of skin permeation enhancer in ndds.

SR. Nos.	Patent Number	Inventor	Current Asignee	Tittle Description	Publication Date

					(Grant)
1.	US4704282A US Grant	Patricia S Campbell, James B Eckenhoff or Patricia S. CampbellJames B. Eckenhoff	Alza Corp	Transdermal therapeutic system having improved delivery characteristics	1987-11-03
2.	US5925373A US Grant	Spiros A. Fotinos	THALLIUM HOLDING COMPANY, LLC	Transdermal delivery device containing an estrogen	1999-07-20
3.	EP0316065A2 EP Application	Eun Soo LeeSu Il Yum	Alza Corp	Improved transdermal drug delivery device	1993-05-26
4.	US5071657A US Grant	Horst Oloff, Johannes-Wilhelm Tack, Fred Windt, Ingfried Zimmermann	Bayer Pharma AG	Device for transdermal administration of active medicinal agents	1991-12-10
5.	US5318960A US Grant	Frank Toppo	TOPPO ROBERT J	System for transdermal delivery of pain relieving substances	1994-06-07
6.	US5498417A US Grant	Ramesh Lhila, Stuart Ganslaw, Eleanor Serra	Coating Sciences Inc	Transdermal delivery of appetite suppressant drug	1996-03-12
7.	US5527832A US Grant	Sang-Cheol Chi, Hyun-Kwang Tan, Heung-Won Chun	Il-Dong Pharm Co Ltd	Antiinflammatory and analgesic transdermal gel	1996-06-18
8.	US5562917A US Grant	Franck Durif, Ragab El-Rashidy	Pentech Pharmaceuticals Inc	Transdermal administration of apomorphine	1996-10-08
9.	US5817332A US Grant	Arto O. Urtti, Marja R. Sutinen, Timo P. Paronen	Orion Corp	Transdermal drug delivery system	1998-10-06
10.	US6132760A US Grant	John C. Hedenstrom, Michael L. Husberg, Shari L. Wilking, Matthew T. Scholz	3M Innovative Properties Co	Transdermal device for the delivery of testosterone	2000-10-17

CONCLUSIONS

Novel drug delivery system is opening prospective future in pharmaceutical sciences. It is novel approach for drug delivery which we can achieve better therapeutic action, better bioavailability, reduce toxicity. Today nanoparticles are successfully used in enhance skin penetration, cancer therapy etc. The mention skin permeation enhancer a technique is used to targets the diffusivity of drug's active compound to and through the skin barriers for a range of therapeutic purpose.

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