

The Impact of Penetration Enhancers on Transdermal Drug Delivery System: Physical and Chemical Approach

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ABSTRACT

There is considerable interest in the skin as a site of drug application for both local and systemic effect. However, the skin, in particular the stratum corneum, possesses a formidable barrier to drug penetration thereby limiting topical and transdermal bioavailability. Skin penetration enhancement techniques have been developed to improve bioavailability and to increase the range of drugs for which topical and transdermal delivery is a viable option. Transdermal drug delivery system (TDDS) having objective to deliver the therapeutic moiety via the skin into the systemic circulation for its therapeutic effect. This route provides many advantages over other routes as avoiding first pass hepatic metabolism, decrease side effects, GI effects and increased bioavailability. The skin, in particular stratum corneum provides protective barrier that prevents the loss of physiologically essential substances and provide resistance to penetration and it is the rate limiting step in percutaneous absorption. So, various penetration enhancers have been used to promote the percutaneous absorption of a number of drugs. Several research studies have been done in transdermal permeation studies using various enhancers for several drug moieties. This review high lights the detailed role of penetration enhancers and describes the classification of different penetration enhancers with their mechanism of action and properties. Most of the earlier reviews have focused on a certain selected aspect of transdermal drug delivery. This review presents a comprehensive account of various aspects of drug delivery by transdermal route including the various chemical and physical penetration enhancers.

Keywords: electroporation, iontophoresis, penetration enhancers, percutaneous absorption, stratum corneum

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INTRODUCTION OF TDDS

Transdermal drug delivery system is defined as the topically administered medications, which when applied to the skin deliver the drug, through the skin at a predetermined and controlled rate. The transdermal route has vied with oral treatment as the most successful innovative research area in drug delivery, as oral treatment involves maintenance of drug concentration in the body within a therapeutically effective range by introduction of fixed dose at regular intervals. Due to which drug concentration in body follow a peak and trough profile leading to greater chance of adverse effects or therapeutic failure. Large amount of drug is lost in vicinity of target organ and close

attention is required to monitor therapy to avoid overdosing. More recent advances have concentrated on the development of non-passive systems to aid delivery of larger drug molecules such as proteins and nucleotides as the trend for discovering and designing biopharmaceuticals continues improvements in transdermal delivery will remain incremental until there is wider acceptance of this route of administration within the pharmaceutical industry. However, with continuous exploration of the structure, function, and physicochemical properties 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. The search for the ideal skin penetration enhancer has been the focus of considerable research effort over a number of decades. Although many potent enhancers have been discovered, in most cases their enhancement effects are associated with toxicity, therefore limiting their clinical application. In recent years, the use of a number of biophysical techniques has aided in our understanding of the nature of the stratum corneum barrier and the way in which chemicals interact with and influence this structure. A better understanding of the interaction of enhancers with the stratum corneum and the development of structure activity relationships for enhancers will aid in the design of enhancers with optimal characteristics and minimal toxicity [1-3].

Advantages of TDDS:

- Avoid the first pass metabolism of drugs.
- Adverse effects or therapeutic failures frequently associated with intermittent dosing can also be avoided.
- The simplified medication regimen leads to improved patient compliance and reduced the side effects.

- It increases the therapeutic value of many drugs via avoiding GI irritation, lower absorption, decomposition due to 'hepatic first pass' effect.
- This route is suitable for the administration of drugs having very short half life, narrow therapeutic window and poor oral availability.
- Improved patient compliance and comfort via non-invasive, painless and simple application.

Disadvantages of Transdermal drug delivery system:

- Local irritation may develop at the site of application.
- A drug has large molecular size makes absorption difficult. So drug molecule should ideally be below 800-1000 daltons.
- Many drugs with a hydrophilic structure having a low penetration through the skin and slowly to be of therapeutic benefit.
- Transdermal drug delivery system cannot achieve high drug levels in blood.

Advantages & Disadvantages of penetration enhancers:

Table 1: Advantages & Disadvantages of penetration enhancers [3]

Advantages	Disadvantages
1. Penetration rate of drug sufficiently high for therapeutic efficiency by using penetration enhancers.	1. The effective concentration varies from drug to drug.
2. It is useful for unabsorbable drugs to facilitate their absorption through skin.	2. The uses of different penetration enhancer with various concentrations are restricted completely.
3. It can improve transdermal absorption of topical preparation.	
4. It is penetration rate determining factor in transdermal drug delivery system.	3. Physicochemical properties of enhancers are also affecting the side effects in the body.
5. The terpenes like limonene in propylene glycol solution are effective penetration enhancer for cytotoxic drugs.	
6. It also acts as rate limiting factor.	

This review article includes various aspects of transdermal drug delivery including various enhancers and permeation studies are considered. Methods of studying enhancer mechanisms and skin toxicity of enhancers are also discussed [4-6].

Drug delivery across the skin:

The skin basically consists of three anatomical layers as shown in **(Figure 1)**

- The epidermis, which is a thin, dry and tough outer layer, itself made of several layers consisting of two main parts: the stratum corneum (SC) and the stratum

germinativum; the most superficial layer is the SC which is formed and continuously replaced by stratum germinativum.

- The dermis, which is the thick sensitive layer of skin or connective tissue that

contains blood, lymph vessels, sweat glands and nerve endings.

- The subcutaneous fatty layer, which contains fatty layer and act as an insulator and depot of calories [1, 2].

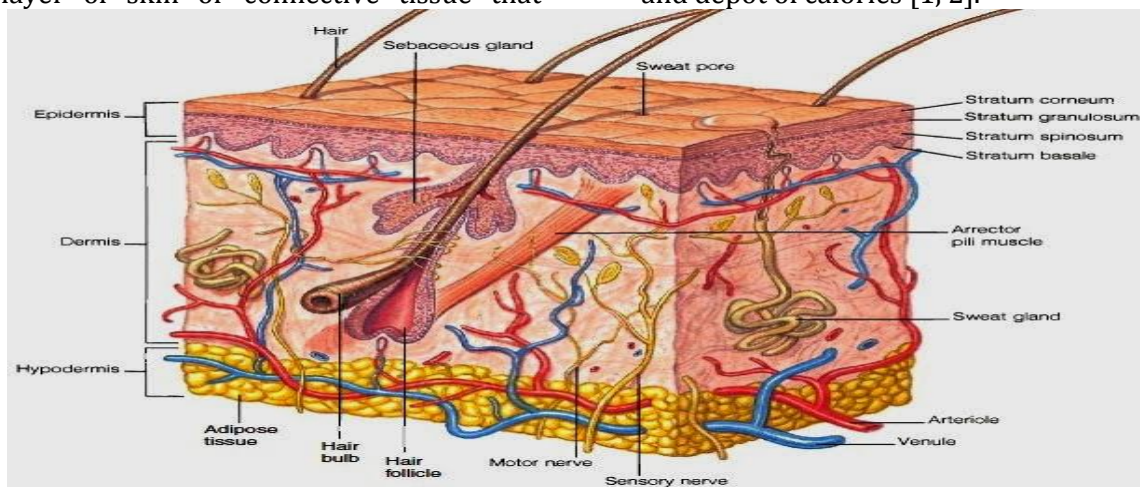


Figure 1: Anatomy of skin

Ideal properties of penetration enhancers: [2, 3]

- 1.The effect of enhancer on the skin should be reversible, and it should not damage the cells.
2. It should be pharmacologically inert.
- 3.It should not be toxic, allergenic and irritating.
4. It should not be incompatible with the drug and excipients.
5. It should show rapid and predictable effect.
- 6.It should have unidirectional enhancing effect allowing the drug molecule to pass through the skin.
- 7.During penetration preventing the loss of endogenous materials like body fluids, electrolytes.

Function of permeation enhancer:

On the basis of lipid protein partitioning concept, there are three main functions of penetration enhancers, Lipid disruption: The enhancers change the structure of stratum corneum lipid organization and make it permeable to drugs. Many enhancers operate mainly in this way e.g. Azone, terpenes, fatty acids, dimethylsulfoxide (DMSO) and alcohols.

Protein modification: Ionic surfactants, decylmethylsulfoxide and DMSO interact with keratin in corneocytes and open up the dense protein structure and make it more permeable.

Partitioning promotion: Many solvents change the solution properties of the horny layer and increase the partitioning of a drug, co enhancer and co solvent [7-9].

Routes of penetration across the skin:

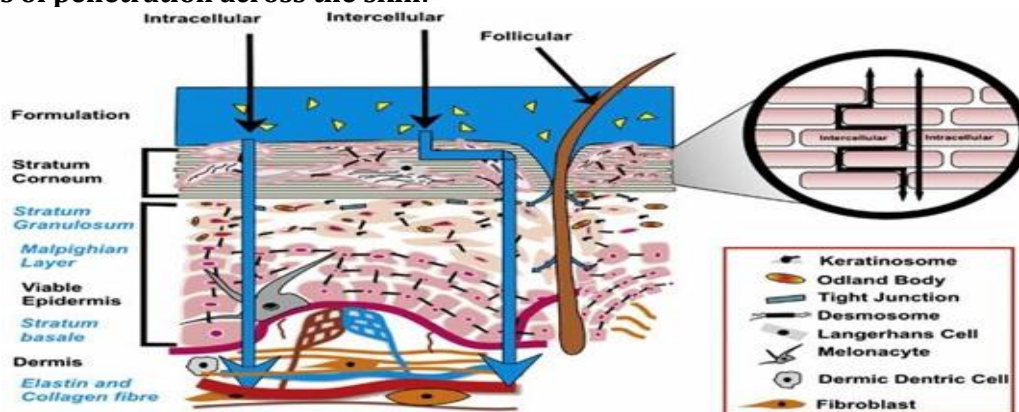


Figure 2: Routes of Penetration enhancers

There are three potential pathways through which drug molecules in contact with the skin surface can penetrate 1) through the sweat ducts 2) through the hair follicles 3) sebaceous glands (collectively called the shunt or appendageal route) or directly across the SC. It is generally agreed that appendages contribute for permeation of drug is minimal approximately 0.1%. Thus the SC is the most important route for most drug skin penetration. Conventionally, it is thought that lipophilic compounds transfer preferably into the lipoidal intercellular phase of the SC while relatively more hydrophilic compounds transfer into the intracellular domain. The intercellular route is now considered to be the major pathway for permeation of most drugs across the SC. Thus most of the techniques to optimize permeation to drugs across the skin are directed towards manipulation of solubility in the lipid domains [8, 9].

Permeation mechanism of TDDS:

The penetration enhancers may show their effect any one or combination of the following mechanisms.

- By disrupting the structure of stratum corneum lipids.
- By interacting with intercellular proteins.

- By improving drug partitioning, co-enhancer or solvent into the stratum corneum.
- Dissolution of drug in its vehicle.
- Diffusion of drug from vehicle to surface of skin.

The chemical enhancers show their enhancing effect by bringing alterations in, at least any one three pathways. The polar pathways are altered by solvent swelling or conformational changes in proteins. The fatty acids show their effect by increasing the fluidity of lipid protein portion of the stratum corneum. Some enhancers act on both polar and pathways by altering the multilaminar penetration pathway [5-9].

The following equation for the penetration rate (flux) explains the factors which could affect the drug permeation rate.

$$dm/dt = D C_0 K / h$$

Where;

dm/dt = steady state flux

C_0 = constant concentration of the drug in the donor solution

D = diffusion coefficient

h = membrane thickness

K = the partition coefficient of the permeant between the membrane and the bathing solution.

Types of penetrations enhancers or Classification of penetrations enhancers:

Table 2: Classification of penetration enhancers [5]

Sr. No.	Types of penetration enhancers	Mechanism of action	Techniques of penetration enhancers OR Examples
1	Physical Enhancers	Rate control over the release and transdermal permeation of drugs	1. Iontophoresis 2. Sonophoresis 3. Phonophoresis 4. Magnetophoresis 5. Electroporation 6. Thermophoresis 7. Radiofrequency 8. Needleless injection
2	Chemical enhancers	Interrupt structure of stratum corneum lipid Interaction with intercellular protein Improved partition of the drug or	<ul style="list-style-type: none"> • Surface-active agents– Sodium lauryl sulphate(SLS), Benzalkonium chloride • Cyclodextrins • Amine and Amides • Azones • Pyrrolidones • Sulphoxides– Dimethylsulphoxides(DMSO), dimethylformamide(DMF), dimethyl acetamide(DMAC)

		solvent into stratum corneum	<ul style="list-style-type: none"> • Fatty acids– Lauric acid, Myristic acid, Capric acid
3	Natural Penetration Enhancers	<ul style="list-style-type: none"> • Partition coefficient • Diffusion coefficient • Lipid Extraction • Drug Solubility • Molecular orientation of terpenes molecule with lipid bilayer 	<ul style="list-style-type: none"> • Terpenes–Menthol, Linalool, Limonene, Carvacrol. • Essential oil–Basil oil, Neem oil, Eucalyptus, Chenopodium
4	Drug Vehicle Based	Oppositely charged species to a charged drug, formation of an ion pair in which charges are neutralized so drug permeate through the stratum corneum	Ion pairs and complex coacervates chemical potential adjustment

Approaches Used for enhancement of Drug in TDDS:

Physical approaches:

Iontophoresis: The iontophoresis is the process which involves increased transport of solute molecules into a tissue using an electric current. Due to the highly lipophilic nature of skin resist the permeation of hydrophilic, high molecular weight and charged compounds through the stratum corneum into the systemic circulation. Iontophoresis is external source of energy in the form of an applied direct electric current. Electrical energy is responsible for the movement of ions across the stratum corneum. The principle of iontophoresis

technique is based on that the like charges repels each other and opposite charge attract. Thus during iontophoresis, if delivery of positively charged drug, the charged drug is dissolved in the electrolyte surroundings the electrode of similar polarity, i.e. anode. An application of electromotive force the drug is repelled and moves across the stratum corneum towards the cathode, which is placed elsewhere on the body. When cathode is placed in the donor compartment of the Franz diffusion cell to enhance the flux of an anion, it is termed cathode iontophoresis and for anodal iontophoresis the situation would be reversed [9, 10].

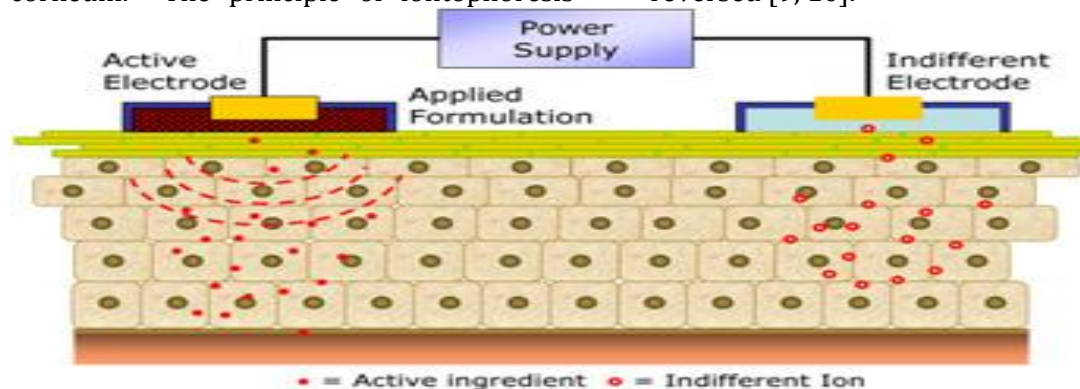


Figure 3: Drug penetration through Iontophoresis

Mean principal mechanism by which iontophoresis enhances molecular transport across the skin are: 1) Charged ion is repelled from an electrode of the same charge. 2) Electro-osmosis; the convective movement of solvent that occurs through a charged pore in response to applied electric field. 3) Flow of electric current increase the permeability of the skin. 4) The interaction of ion and electrical field provides the directional force which drives ions through the skin. [11, 12]

Factors affecting iontophoresis:

Molecular size and molecular weight:

Smaller and more hydrophilic ions are transported at faster rate than the larger ions. When the molecular size increases, the permeability coefficient decreases.

Concentration: An increase in concentration was increase the flux of the drug.

Ionic strength: The ionic strength of drug delivery system is proportional to the Iontophoretic permeation of drugs.

Charge: Molecular charge is an important physicochemical property control

iontophoretic transport. Increase in the charge will require pH to be decrease, which in turns directly decreases the electro-osmosis and electro transport process.

Current strength: In Iontophoresis constant direct current has been used. There is linear relation between the fluxes (1cm^2); the current (1mA) for the patient comfort. This current should not apply for more than 3 min because of local skin irritation and burns. With increasing current, the risk of non specific vascular reactions increased. In general, $0.5\text{mA}/\text{cm}^2$ is often stated to be the maximum iontophoresis current.

Electrode material: The most common electrodes are aluminum foil, platinum and silver-silver chloride electrode used. Electrode Ag/AgCl are the most preferred as the resist the change in pH which is generally seen during the use of platinum or Zn/ZnCl electrodes. The position of electrodes depends on charge of drug. The drug distribution depends on size and position of electrodes [13].

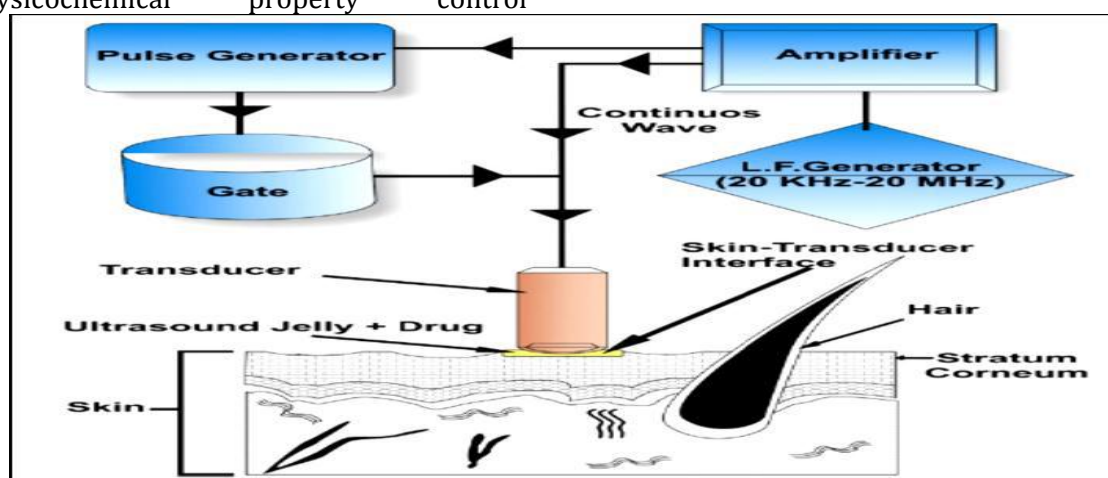


Figure 4: Drug penetration through sonophoresis

Another technique attempting to overcome the challenges of transdermal drug delivery involves the usage of high or low frequency ultrasound waves. The enhancements in drug penetration result from enhanced diffusion due to ultrasound-induced skin alteration. Ultrasound alters the skin porous pathways by two mechanisms: (1) enlarging the skin pores (2) creating more pores. Absorption of ultrasonic energy leads to tissue heating, and this has been used with therapeutic intent in many conditions.

Ultrasound therapies with low power sonophoresis, sonoporation, gene therapy and bone healing. Mechanism of action of sonophoresis is that due to cavitations occur in stratum corneum due to ultrasound exposure and penetration is occur which is now increases up to 5,000 times in insulin delivery [15, 16].

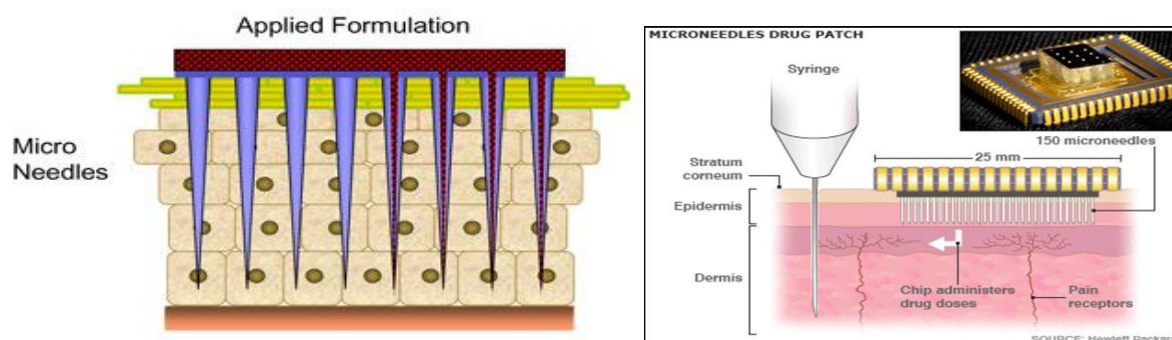
Table 3: Advantages and disadvantages of sonophoresis [17, 18]

Advantages	Disadvantages
1) Allows control transdermal penetration rates and permits rapid termination of drug delivery through ultrasound technique with low immunological sensation.	1) Time consuming technique.
2) Avoiding the hepatic first-pass effect.	2) Burning and irritation has been observed in some cases.
3) Skin remains intact, therefore low risk for infection.	3) Proper and control adjustment of ultrasound waves is required to avoid above side effect.
4) Drug penetration through the passive transport	

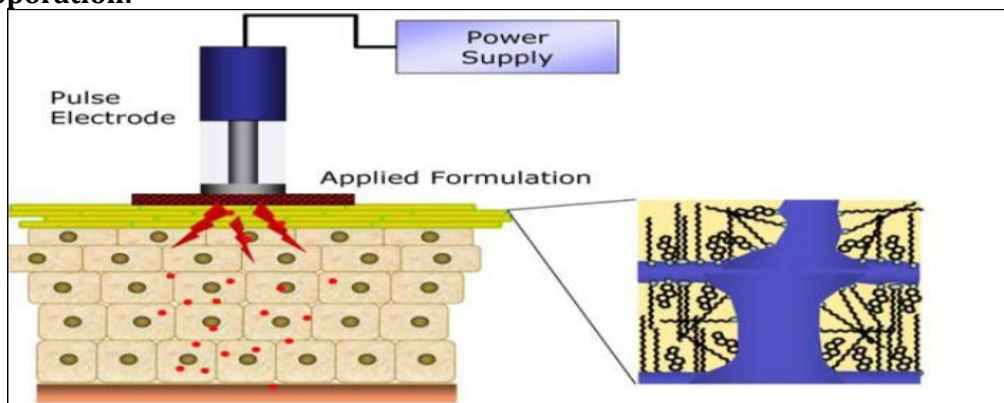
Microneedle Technology:

The microneedles technology employs micron-sized needles made from silicon. Microneedles have been fabricated with different range of size, shape and materials. Penetrate the upper layer of skin without reaching the dermis, to be an efficient method to deliver drugs transdermally in an

almost painless method. Mechanism of action of microneedles penetrates the stratum corneum and epidermis to deliver the drug from the reservoir. The reservoir may contain drug, solution of drug, gel, solid particulates, enclosed in membrane to separate the drug from the skin and control release of the drug from its reservoir.

**Figure 5: Drug penetration through microneedles [19]****Table 4: Approaches of microneedles [18, 19]**

Approaches through Micro needle	Mechanism of action	Applications of Micro needles
Poke with patch approach	Through micro pore drug enter In to the lower layers of the epidermis.	Insulin delivery
Coat and poke approach	By inserting the microneedles through the skin, the drug coating dissolves off in the skin fluid and drug diffuses through the skin into the blood circulation.	Delivery of nanoparticles
Dip and scrape	Placing the array in contact with the drug solution and then scraping multiple times across the skin to create micro abrasions.	Acne treatment
Injection through hollow microneedles	Openings through which drugs are microinjected and then diffuse into the lower layers of the skin dermis.	Cutaneous fluid extraction and glucose monitoring.
Dissolving microneedles	Encapsulated drug is released in a controlled manner as the microneedles dissolves off when inserted into the skin	Vaccination against virus

Electroporation:**Figure 6: Drug penetration through electroporation**

Electroporation is the phenomenon in which cell membrane permeability to ions and macromolecules is increased by exposing the cell to short high electric field pulses. Due to electric field breakdown of the cell membrane and the formation of pores in the membrane and hence called as electroporation. The mechanism for electroporation by two pathways, through pores formed in the multiple lipid bilayer connecting corneocytes and through appendage cells. The efficacy of transport of drug depends on the electrical parameters and the physicochemical properties of drugs. For introduction of DNA is the most common use for electroporation also it has been used on isolated cells for introduction of enzyme, antibodies and viruses and more recently, tissue electroporation has started to be for cancer tumor chemotherapy, gene therapy and transdermal drug delivery.[16]

Magnetophoresis:

Magnetophoresis is a novel approach in enhancing drug delivery across biological barriers. The influence of magnetic field strength on diffusion flux was determined. Due to the magnetic field which acts as an external driving force to enhance the diffusion of a solute across the skin. Exposure of a magnetic field induces structural alterations that could contribute to an increase in permeability. In vitro studies showed a magnetically induced enhancement in benzoic acid flux, which was observed to increase with the strength of the applied magnetic field. [17]

Phonophoresis:

Utilization of ultrasound to enhance the delivery of topically applied drugs.

Phonophoresis has been used in an effort to enhance the absorption of topically applied analgesics and anti-inflammatory agents through the therapeutic application of ultrasound. Phonophoresis has been shown to be ineffective regarding some drug, where it did not increase the efficacy of absorption of drugs, or did not improve the outcome more than the use of ultrasound alone. In the majority of the studies on phonophoresis was used to enhance the delivery of steroidal anti-inflammatory drugs. [20]

Chemical approach:

Chemical penetration enhancers insert themselves directly between the hydrophobic lipid tails and change lipid packing which cause fluidity of lipid and enhance the drug permeation. These penetration enhancers referred as absorption promoters or accelerants.

Surface-active agents:

A substance which is positively adsorbed at the liquid or vapour or at other interfaces is called surfactants. Following are the classes of surfactant (Table 5) [21-25].

Cyclodextrins:

It is well known that cyclodextrins can enhance the permeation of poorly soluble drugs through biological membranes. The permeability will decrease if cyclodextrins is added in excess of the concentration needed to solvate the drug. The effect of cyclodextrins cannot be explained as solely due to increased solubility of the drug in the aqueous donor phase. Cyclodextrins act as classical permeation enhancers, by decreasing the barrier function of the lipophilic membrane. It acts as permeation enhancers carrying the drug through the

aqueous barrier, from the bulk solution towards the lipophilic surface of biological membranes, where the drug molecules partition from the complex into the

lipophilic membrane. Cyclodextrins complexes with number of drugs usually enhance the permeation of drug. [26, 27]

Table 5: Classes of surfactant

Class of surfactant	Mechanism of action	Example	Factor affecting on drug penetration
Anionic	Interact strongly with both keratin and lipids. Change the permeability of the skin by acting on the helical filaments of the stratum corneum, thereby resulting in the uncoiling and extension of keratin. Then they cause an expansion of the membrane, which increases permeability	Sodium lauryl sulphate(SLS)	Critical micelle concentration
Cationic	The cationic surfactants interact with the keratin fibrils result in a disturbed cell-lipid matrix. These surfactants interact with anionic components of the stratum corneum, change the property, and stimulate the transfer of the anionic drug into the skin	Akylamido dimethyl propylamine	Chain length of carbon atoms
Nonionic surfactants	1) Penetrate into the intercellular regions of SC increase fluidity. 2) Interaction and binding with keratin filaments may results in a disruption within the corneocytes.	Polyethylene glycol ester	Transdermal gradient
Amphoteric	Solubilization of stratum corneum lipids an important mechanism of penetration enhancement. When a surfactant molecule exhibits both anionic and cationic dissociations it is called Amphoteric or zwitterionic.	Acylamphoacetate	Steric forces

Azones:

Mechanism of action of azone, increasing the fluidity of the intercellular lipid bilayer of the stratum corneum. Azone was the first molecule or agent which was specifically designed as a skin penetration enhancer. Azone partitions into the bilayer lipid for disrupting their packing arrangement. It may exist as dispersed within the barrier lipid or separate domains within the bilayer. Azone possesses a smooth, oily but yet non greasy feel. It is a colorless, odorless liquid with a melting point of -7 °C. Azone is a highly

lipophilic material and it is also compatible with the most organic solvents including alcohol and propylene glycol. [28] It increased the skin transport of a wide variety of drugs including steroids, antibiotics and antiviral agents. Azone is basically most effective at low concentration. Usually it is used typically between 0.1- 5% but more often between 1- 3%. [30-32]

Sulphoxides: Dimethylsulphoxides (DMSO) is one of the earliest and most widely studied penetration enhancers. It is a powerful aortic solvent which hydrogen

bonds with itself rather than with water. It is colorless, odorless and is hydroscopic and is often used in many area of pharmaceutical sciences as a universal solvent [21]. DMSO alone has been applied topically to treat systemic inflammation. Dimethyl sulphoxides (DMSO) and decylmethyl sulphoxides (DCMS) are used widely as skin permeation enhancer and co-solvent. These types of penetration enhancers change the water structure with in cell. The mechanism of the sulphoxides penetration enhancers is widely used to denature protein and on application to human skin. [33-37]

CONCLUSION

In order to increase the range of drugs available for transdermal delivery the use of chemical and physical enhancement techniques have been developed in an attempt to compromise skin barrier function in a reversible manner without concomitant skin irritation. Several alternative physical methods have emerged to transiently break the stratum corneum barrier and also the use of chemical enhancers continues expanding. Microneedle arrays are inserted through the skin to create pores through which pores drug penetrate in to skin. Microporation creates arrays of pores in the skin by heat and radio frequency. Skin penetration enhancers are rapidly using technique for the permeation of drugs through the skin by transdermal drug delivery system. Different approaches are applied like physical enhancers, chemical enhancers, natural enhancers etc. These approaches are very useful for the drugs having low permeable property, low soluble drugs and for the drugs having short biological half life.

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