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Connotation of Incorporation of Penetration Enhancers in Topical Drug Delivery- A Review

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ABSTRACT

Topical drug delivery is most acceptable and convenient route of administration of drug which are having short half and which are poorly soluble drugs. Along with its topical route also set to be a challenging area for the delivery of drugs through stratum corneum. Traditionally permeation enhancers were designed to deliver drug molecules across the skin into the systemic circulation. The emergence of some other techniques for enhancement through modification of stratum corneum by hydration, or by using chemical or physical effects has remained an area of interest. In this review, were presented an overview of the current strategies to overcome stratum corneum as a barrier for entry of drug molecule.

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INTRODUCTION

The transdermal route now ranks with oral treatment as the most successful innovative research area in drug delivery, with around 40% of the drug delivery candidate products under clinical evaluation related to the transdermal or dermal system. First, the skin is an excellent permeability barrier refractive to nearly all but small lipophilic molecules, as is discussed briefly further in the text (Vineet Mathur *et al*, 2010)**.** Drug delivery via the percutaneous route potentially has many advantages over intravenous and oral administration. The principal barrier to topical drug delivery is the stratum corneum which possesses a formidable barrier to drug penetration thereby limiting topical and transdermal bioavailability (Mohammad Aqil *et al***,** 2009)**.** Transdermal drug delivery is the administration of a therapeutic agent through intact skin for systemic effect the method employed for modifying the barrier properties of the stratum corneum to enhance drug penetration and absorption through skin may be classified into the following categories:

1. Chemical enhancement
2. Physical enhancement
3. Biochemicalenhancement
4. Supersaturationenhancement

5. Bioconvertable pro drug **(**Pathan IB & Setty CM 2009 & Saini S *et al* 2014) Penetration enhancer used to increase the permeability of drugs through the skin.

Ideal properties of penetration enhancers

1. They should be non-toxic, non-irritating, and non-allergenic.
2. It should be cosmetically acceptable**.** It should physically and chemically stable also.
3. Should be compatible with drug and excipient.
4. It should have no pharmacological activity within the body.
5. It should be odorless tasteless colorless and inexpensive and have good solvent property. **(**Sushila Saini *et al* 2014). They would ideally work rapidly; the activity and duration of effect should be both predictable and reproducible.

1) When removed from the skin, barrier properties should return both rapidly and fully to normal. (Pathan IB & Setty CM2009).

Mechanism of action of penetration enhancers

Skin permeation enhancer may exert their effect through one of the combinations of the following mechanism:

1. By solubilizing the skin tissue component.

2. Interaction with intracellular lipids leading to disruption with highly ordered lamellar structure.

3. Interaction with intracellular proteins to promote permeation of the drugs through the corneocyte layer.

4. Improved partition of the drugs, co-enhancers, co-solvents into stratum corneum. (Patil UK & Saraogi R, 2014).

5. Decomposing the lipid bilayer anatomy in the stratum corneum (SC) and thereby enhancing the drug's diffusion coefficient extracting lipids from the stratum corneum.

6. Reorienting the solvent nature of the SC and inevitably modifying the drug partitioning coefficient, acting on subcellular keratin, etc.

7. Enhancers can augment the drug diffusivity through skin proteins.

8. The type of enhancer engaged has a noteworthy impact on the design and development of the formulation.

9. Fatty acid radical enhancers increased the runniness of the lipid-protein segment of the stratum corneum. (Barry BW 1983).

It is well known as that the stratum corneum lipids provide the primary barrier function of the skin. Therefore, it would be pertinent to understand their organization to fully elucidate the mode of action of permeation enhancer (Charles AB *et al* 2000). Different Penetration Enhancers have a 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 the skin. (Saini S *et al*, 2014).

Objectives of using penetration enhancers in transdermal delivery

The ultimate goal of transdermal drug delivery is to ensure that compounds are delivered, preferably at a specific rate, to the systemic circulation. Penetration of drug to the dermal vasculature follows exposure of the skin to a dosage form from which the action must partition, followed by diffusion of the compound through the external strata to the dermis. Partitioning of the drug from the dosage form is highly dependent on the relative solubility of the drug in the component of the delivery system and the stratum corneum. (Walker RB & Smith EW, 1996).

Mechanism of penetration enhancers

Based on lipid-protein partitioning concept, there are three main functions of penetration enhancers.

1. Lipid disruption: The enhancers change the structure of stratum corneum lipid organization and makes it permeable to drugs. Many enhancers operate mainly in this way [e.g. Azone, terpenes, fatty acids, dimethyl sulfoxide (DMSO), and alcohols.

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

3. Partitioning promotion: Many solvents change the solution properties of the horny layer and thus increase the partitioning of a drug, enhancer, and cosolvent. Ethanol increases the penetration of nitroglycerin and estradiol through the stratum corneum. (Sudhir K *et al*,2012).

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 relative importance of the shunt or appendageal route versus transport across the stratum corneum has been debated by scientists over the years and is further complicated by the lack of a suitable

experimental model to permit separation of the three pathways.

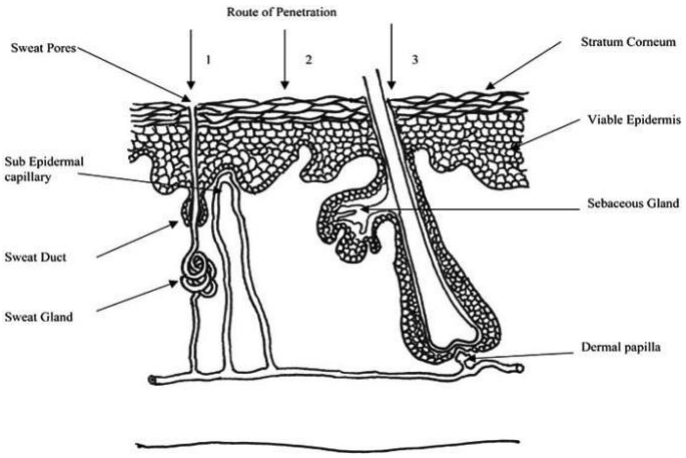

Figure No. 1: Simplified representation of skin showing routes of penetration: 1. through the sweat ducts; 2. directly across the stratum corneum; 3. via the hair follicles (Heather B, 2005)

The Intercellular pathway:

Penetration between SC corneocytes is the pathway by which most compounds penetrate the skin. Most skin penetration enhancers were found to affect the intercellular lipid bilayers of which this route consists.

The Intrafollicular pathway

The amount of sebaceous glands on the total skin surface represents not more than 0.1%. Therefore some scientists believe that this route is not a significant penetration pathway for most molecules. When considering these openings as a possible route for penetration, it is important to understand the variations in follicle distribution among different body locations.

The polar pathway

This route is believed to be hydrophilic. It is composed of aqueous regions surrounded by polar lipids that create the walls of microchannels. It is known to have a high penetration resistance to lipophilic compounds but low resistance to hydrophilic compounds. (Nava D, 2005).

Stratum corneum as a barrier to drug permeation

Stratum corneum hydration is essential for the proper function and appearance of the skin. The moisture content can be measured *in-vitro* utilizing gravimetric or electron microscopy, or by magnetic resonance techniques *in-vivo*. Their solution of the latter technique is, however, currently not sufficiently high to enable isolated measurements on the stratum corneum. Compared with these techniques, assessment of stratum corneum hydration utilizing electrical measurements (susceptance) represents an important reduction in instrumental cost and complexity. (Grimnes S and Martinsen Ø, 2015).

The penetration enhancer divided into four types:

1. Physicalenhancers
2. Chemical enhancers
3. Natural enhancers
4. Miscellaneous enhancers

Table No. 1: Techniques and examples of penetration enhancers

Physical Enhancers	Chemical Enhancer	Natural Enhancers	Miscellaneous Enhancers
Iontophoresis	Sulphoxides	Cineole	Capsaicin
Sonophoresis	Azones	Eugenol	Vitamin E
Magnetophoresis	Pyrrolidone	D-Limonene	Phospholipids
Thermal Energy	Amines And Amides	Menthol	Lipid Synthesis Inhibitors
Electret EnhancesTDDS	Oxazolidinone	Basil Oil	Clofibric Acid
Needleless injection	Fatty Acid An Ester	Clove Oil	----
Laser ablation	Surface active agents	Capsaicin	-----
Mechanical Perturbation	----	----	----
Jet propelled particles	----	----	----
Microfabrication Microneedle technologies	----	----	----

1) Physical enhancers

To improve the penetration ability of agents therapeutics into the systemic circulation, numerous methodologies have been investigated, developed and patented such as physical enhancers: iontophoresis, Sonophoresis, Magnetophoresis, Thermal Energy., Electret enhances TDDS, Laser ablation, Mechanicalperturbation, Jet-propelled particles, Microfabrication microneedles technologies.

A) Iontophoresis

In this technique, small electrical current across the skin is applied to deliver ionized drug molecules and peptides at a faster rate than normal. Essential, the charged molecule is forced into the stratum corneum as it is repelled from the electrode of similar polarity. (Longsheng H *et al*, 2010) Due to force exerted by the electrical current drug molecules are forced to permeate inside the skin. There is the various mode of actions which have been anticipated for faster permeation Reena R*et al* (2005) & Preat V*et al* (2003).

i) The electric current damages the protective nature of the skin.

The drug is forced into the various layers of skin by anode-cathode charge development. Anionic charge moves to the cathode, whereby cationic charge shifts to the anode. Bogner *et al* (1994).It is a preconception that this method facilitates the congeries of water by electroosmosis, which results in hydration of skin and drug penetration is enlarged due to better-hydrated condition of skin Pikal MJ *et al* (2001).

B) Sonophoresis

Sonophoresis is the movement of drug molecules through the skin under the influence of ultrasound. His technique typically uses a low-frequency pressure wave of less than 100kHz.The application of ultrasound to the skin can disrupt the stratum corneum lipid bilayer. As a result, drug molecules are allowed to permeate through the skin more easily. The combination of sonophoresis and iontophoresis significantly enhanced the transdermal delivery of certain drugs. (Longsheng H *et al*, 2010).

Many theories are particularizing the transcytosis of hydrophilic permeants in the presence of ultrasound. Mitragotri S (2004).

Congruent microscopy indicates that hollow point occurs in the keratinocytes of the stratum corneum upon ultrasound subjection Mitragotri S (2004).

Recent research work has manifested that ultrasound can increase up to 5,000 times the ability of protein the size of insulin to penetrate the skin.

Using a transdermal patch design in concurrence with ultrasound may provide an improved method for insulin delivery. The enhancement may result from enhanced diffusion due to ultrasound-induced skin remodeling and/or from forced convection. Rao R, Nanda S (2009) and Escobar CJJet al (2009).

C) Magnetophoresis

Magnetic energy has been used in healing for thousands of years. Magnetophoresis is defined as the motion induced by a magnetic field on a particle of magnetic or magnetizable material. The term Magnetophoresis has also been used to describe the augmentation of drug permeation across a biological barrier by the application of a magnetic field. The enhancement of small molecules has been demonstrated using a range of magnetic technologies including static magnets and pulsed electromagnetic fields. The magnetic arrays used in static or moving mode offer advantages concerning the fabrication of devices. These can be incorporated into a transdermal patch or used as an applicator for a topical cream or gel. (Heather AE, 2017) The influence of magnetic field strength on diffusion flux was determined and was found to extension with increasing applied field muscularity. Murthy SN (1999).

D) Thermal Energy

Heat influences the permeability of blood vessels wall, which in turn increases total fluid circulation. Due to an increase in total fluid, the permeability of the drug molecules into the systemic circulation is enhanced. Heat also causes some changes in physiochemical properties of patches. Other than this, sweating and hydration of skin are also altered, which help to increase the penetration of drugs. Heat is expected to enhance the transdermal delivery of various drugs by increasing skin permeability, body fluid circulation, blood vessel wall permeability, rate-limiting membrane permeability, and drug solubility. Heat is known to increase the kinetic energy of the drug molecules and the proteins, lipids, and carbohydrates in the cell membrane. Heating before or during the topical application of a

drug will dilate penetration pathways in the skin, increase kinetic energy and the movement of particles in the treated area, and facilitate drug absorption. Heating the skin after the topical application of a drug will increase drug absorption into the vascular network, enhancing the systemic delivery but decreasing the local delivery as the drug molecules are carried away from the local delivery site. (Chauhan SB, 2017).

Electret enhances TDDS: Electret is an electrically charged bakelite disk that conveys semi. Permanent electric charge. It is signalized by the surface potential in volts. Murthy NS (2008).

Electrets and the electret readers used in this study are monetary available under the brand name E-PERM. The active surface of the electret is about 12 cm2. The electret bestows surface potentials from500 to 3000 V, easily quantifiable using an electret reader. Electret was hinge to enhance the penetration of hydrophilic drugs (but not lipophilic drugs) beyond the skin.

However, the electret effect dematerializes when the moisture content in the formulation expands. The surface voltage of electret was not exempted significantly by the presence of white petroleum jelly glazing on the E-PERM electrets. It is also attainable to use a thin layer of removable uncharged bakelite to cover the facet of the electret this allows the electric field to go through and at the same time safeguards the electret surface from getting adulterated. Cui Let al (2001).

Needleless Injection: It is one of the renowned proficiency since it does not entail any pain and discomfort (irritation) to the patient. It is a highly enlightened technique whereby liquid and solid particles are cannonade at supersonic speed into the skin. Burkoth TL (1999).

The technique utilizes compressed gases such as nitrogen or helium through a narrow nozzle along with the drug molecules in a jet flow. Jones S, Brown MB (2005). But the complications corresponding with this method are high development cost for dosage form development and to control the device once initiated due to variations in skin permeability. Long BDJ et al (1998).

Laser ablation: The use of lasers (rays) to remove the stratum corneum blockade by controlled ablation has also been scrutinized as a means of enhancing topical drug delivery

Jacques SL (1987).This method involves direct and controlled subjection of a laser beam to the skin which results in the ablation of the stratum corneum without notably destroying the underlying epidermis. It has been also delineating that laser ablation of stratum corneum intensifies the permeation of both hydrocortisone and interferon. Nelson JS et al (1997).

Mechanical perturbation: Microstructured Transdermal Systems empowers the damage of the outermost layer of the skin, the stratum corneum, without causing agony. MTS dilates the range of drugs that can be delivered transdermally and potentially reduces variation in transdermal drug delivery generated by different skin types and application sites. It is accommodated for vaccines, protein, or peptide based drugs. Nanda S & Anand S. (1998).

Jet-propelled particles: The use of constricted gas to force solid drug particles through a convergent divergent nozzle was reported by some scientists using constricted helium. The energy of a mutable helium gas jet speed ups fine drug particles of 20-100 μm diameter to high velocities and delivers them into the skin or mucosal sites. Particle momentum is controlled within the device by three parameters namely nozzle geometry, membrane burst strength, and gas pressure. Preclinical and clinical culminations that best characterize the automation and introduce its potential as a drug-delivery objective. High-velocity powder injectables is a hopeful new drug-delivery method that provides needle and pain-free delivery of orthodox drugs, drugs from biotechnology such as proteins, peptides, and oligonucleotides as well as orthodox and genetic vaccines. Schrammand J, Mitragotri S (2002).

Jet-propelled particle device has been delineated to successfully deliver testosterone, lidocaine hydrochloride, and macromolecules such as calcitonin and insulin. Cross SE & Roberts MS (2004).

Microfabrication microneedles technologies: The microfabricated microneedles technology hires micron-sized needles fabricated from silicon. Shivanand P (2009).

Microneedles have been created with a divergent range of sizes, shapes, and materials. Drug delivery by microneedle enhances skin permeability for a wide range of molecules and nanoparticles.

This microneedle assembly after insertion into the skin produces ducts for the transport of drugs across the stratum corneum. Microneedles inserted into the skin of human subjects were reported as trouble-free. Prausnitz MR (2004) & Henry S et al (1998).

2) Chemical penetration enhancers

Chemical penetration enhancers are utilized in topical preparations as a method for enhancing the permeation of drugs across the skin. In particular, they are utilized for transdermal delivery of medications in an attempt to produce a systemic response, to avoid the first-pass metabolism, and to decrease the gastrointestinal transit time observed with oral medications. A review of the selection of chemical penetration enhancers, their mechanism of action, the most common chemical penetration enhancers in each class, and alternatives will be discussed in detail.

A) Sulphoxides

It is one of the old and widely used penetration enhancers. Due to certain drawbacks of DMSO. Due to this researchers came with the solution of findings of similar chemically related compound as penetration enhancers like Dimethyl acetamide and Dimethylformamide. Sulphoxides are acted as a penetration enhancer by denaturing the protein and thereby to change intercellular keratin configuration. (Saini S *et al*2014).

B) Azone

Azone belongs to the compounds which are specifically designed as transdermal penetration enhancers and prepared during the 70s of the twentieth century (Rajadhyaksha *et. al.* 1976). It contains a lipid alkyl chain and a large polar head group that is thought to be vital for its activity. Due to this it is highly lipophilic material. Increases transport of a variety of drugs which includes mainly, steroids antibiotics and antiviral drugs. It can be used at a concentration of 01-5% to a maximum of 1-3% (Saini S *et al* 2014).

C) Pyrrolidones

Pyrrolidones act as penetration enhancers due to their effects on the intercellular lipid bilayers in the stratum corneum. These enhancers penetrate this region in such amounts that they alter the solubilizing ability of this site, thereby promoting drug partition into the skin. It generally acts by producing reservoir effect which potentiates the sustained release of a permeant from the stratum corneum over extended periods. N-Methyl-2- Pyrrolidone widely used to enhance skin absorption. (R Jayachandra Babu *et al*, 2015).

D) Surface active agents

Surface active agents are generally added to a formulation which helps to solubilize lipophilic active ingredients. So, they can solubilize the lipids within stratum corneum. Function by adsorption at interfaces and thus interact with biological membrane contributing to overall penetration enhancement of compounds. Three types of surface-active agents are Cationic surfactant- Benzalkonium chloride, Cetyltrimethyl Ammonium bromide. Nonionic surfactant- dodecyl betaine. Anionic surfactant- Sodium lauryl sulfate. The function of Anionic and Cationic surfactant is that they swell the stratum corneum and interact with intercellular keratin.

E) Oxazolidinones

Oxazolidinones are a new class of chemical agents that have the potential for use in many cosmetic and personal care product formulations; this is because of their ability to localize coadministered drugs in the skin layers, resulting in low systemic permeation. The structural features of these permeation enhancers closely resemble sphingosine and ceramide lipids, which are naturally found in the upper skin layers. It was proposed that these physical characteristics of the oxazolidinones may be beneficial in terms of a reduction in local toxicity because of the lack of effective absorption of the enhancers into the lower skin layers where irritation is likely to occur (Pathan IB & Setty CM, 2009).

F) Fatty acids and esters

Most fatty acids are straight-chain compounds with carbon chain lengths between 2 and 24. Medium-chain (C6–C10) and long-chain (C12– C24) fatty acids are used as skin penetration enhancers. These have been used as penetration enhancers mainly for lipophilic drugs and to a lesser extent for hydrophilic and peptides. Several patents that describe the utility of fatty acids and their esters or alcohols as enhancers in transdermal formulations have been reported. Similarly, oleic acid and lauric acid induced a 3.5 and tenfold higher permeation of ondansetron HCl as compared to oleyl alcohol and lauryl alcohol, respectively. In another study, oleic acid provided a several-fold higher skin permeation of diclofenac sodium as compared to oleyl alcohol. All these studies indicate that fatty acids are more potent penetration enhancers than fatty alcohols. (Kanikkannn N, 2015).

G) Amines and amides

The effect of amino acids is assumed to be operative via their action upon keratocytes, the effect of esters of omega-amino acids, and epsilon amino acids on the theophylline. Dimethyl acetamide class of amides was the first to be identified as an enhancer, yet it is also a strong irritant. Of the amides of long aliphatic chain several methyls, butyl and isobutyl derivatives of N-dodecyl acetamide proved to be effective. (K. Bauerova *et al*, 2001).

H) Water: Water is the best-revealed penetration enhancer. Hydrated skin better captivates the drug molecules since it increases the flux required for penetration Roberts MS, Walker M (1993). Better the hydration better will be the allowance of penetration elementary technique for upgrading the penetration of drugs through Transdermal patches of the drug molecules. Karande P, Mitragotri S (2009).

3) Natural Enhancers (Essential oils, terpenes, and Terpenoids)

Terpenes are a series of naturally occurring volatile oils which are composed of hydrocarbons and their oxygenated derivatives like alcohols and their glycosides, ethers, aldehydes, phenols, ketones, oxidase, carboxylic acids, and esters. Terpenes are to be clinically acceptable penetration enhancers due to their high percutaneous enhancement ability, the reversible effect on lipids of stratum corneum, less irritancy, and less toxicity. According to skin permeation studies of using diffusion cells and excised animal skin, it was found that terpenes such as 1,8-cineole, menthol, and limonene were effective in enhancing skin penetration. (Patil UK *et al*, 2014)**.**

Essential oils and their constituents may be preferred over the traditionally used synthetics materials as safe and suitable permeation enhancers to promote the percutaneous absorption of hydrophilic and lipophilic drugs from topical formulation into the lower skin layers.

4) Miscellaneous Enhancers (Capsaicin, Vitamin E)

Capsaicin reduces the diffusional resistance of the intercellular domains by inserting itself into the lipid bilayers within the intercellular channels thereby disrupting their stacking. Moderate improvement in the permeability of the stratum corneum can be attributed to the restricted insertion of Vitamin E in the ceramide-rich bilayer structure.

5) Biochemical enhancement: Biochemical enhancement is also another method employed

for moieties like 11-amino acid synthetic peptide obtained by phage exhibit screening Chen Y et al (2006). And a polyarginine heptamer which is connected to the drug by making it prodrug. Ruthord JB et al (2000).

6) Supersaturation enhancement: In this enhancement method increased penetration is achieved by creating an engrossment gradient according to Fick's law. The method presupposes the development and utilization of the thermodynamic potential of the drug. The techniques used to develop supersaturated systems are the expulsion of excess solvents, the reaction of compounds for declining the solubility simultaneous heating and cooling, incorporation of substances which can decline the solubility and results in supersaturation. Daniels R (2004) & Pellet M et al (2003).

7) Bioconvertable prodrug-prodrug approach: Prodrugs refer to the inactive form of the drug, which needs to be organized by metabolism before transfiguring to an active form. The inactive form is more lipophilic than the active form. Higuchi T (1977). A variety of medicaments have been reshaped and delivered through the prodrug approach. Prodrugs of ketorolac have elevated lipophilicity and therefore the increased penetration is attained by percutaneous Drug Delivery.

The prodrug approach has also been used for protein and peptide drug delivery. Tojo K et al (1985).

CONCLUSION:

The efficacy of the penetration enhancer mainly depends on the way which is used to alter the lipid membrane or channels and create the pathways to reach the systemic circulation. The partition coefficient is again very much important in determining the degree of penetration. The penetrants having high lipid solubility can provide more enhancements in bioavailability. It is also found in some literature that the concentration of penetration enhancers also plays a very vital role. As the concentration of the penetration enhancers increases, the drug molecule entry is facilitated, and therefore the drug bioavailability increases. Research in this area has been proved the usefulness of penetration enhancers in the enhancement of drug permeation through the skin. The penetration enhancement methods discussed in this review are the most promising. The focus should be on skin irritation to select penetration enhancers that possess optimum enhancement effects with minimal skin irritation which will ultimately lead to an increase in patient compliance.

REFERENCES:

1. Mathur V, Satrawala Y, Rajput MS (2010): Physical and chemical penetration enhancers in transdermal drug delivery system, Asian Journal of Pharmaceutics, 4(3), 173-183.
2. Mohammad A, Abdul A, Sultana Y, Ali A (2007): Status of terpenes of skin penetration enhancer, Drug Discovery Today, 12: 1061.
3. Pathan IB, Setty CM, (2009): Chemical Penetration Enhancers for Transdermal Drug Delivery Systems, Tropical Journal of Pharmaceutical Research, 8 (2):173-179.
4. Saini S, Chauhan S, Agrawal S, (2014) Recent Development in penetration enhancer and techniques in transdermal drug delivery system, Journal of advanced pharmacy education and research, 4(1):31-40.
5. Patil UK, Saraogi R (2014), Natural products as potential drug permeation enhancer in transdermal drug delivery system, 306 (5), 419–426.
6. Barry BW (1983) Dermatological formulation: percutaneous absorption. Marcel Dekker, NY, USA.
7. Charles SA, Percutaneous penetration enhancers: local versus transdermal activity, Elsevier Science Ltd, 2000.
8. Walker RB, Smith EW (1996): The role of percutaneous penetration enhancers, Advance Drug Delivery Reviews, 18(3):295-301
9. Heather AE, Transdermal Drug Delivery (2005): Penetration Enhancement Techniques, Current Drug Delivery, 2:23-33.
10. Nava D (2005), Pathways for Skin Penetration, Cosmetics & Toiletries magazine, Vol. 120:.68.
11. Raut SV, Nemade LS, Desai MT, Bonde SD, Dongare SU (2015): Chemical Penetration Enhancers for Transdermal Drug Delivery System, Department of Biopharmaceutics, International Journal of Pharmacy Review & Research;4(7):14-24.
12. Sverre Grimnes, Ørjan G Martinsen (2015): Bioimpedance and Bioelectricity Basics Third Edition,Pg.No.110-116
13. Reena R, Srinivas CR (2005) Iontophoresis in Dermatology. Indian J Dermatol
14. Preat V, Vanbever R (2003) Transdermal Drug Delivery (2ndedn.). Marcel Dekker, NY, USA, pp: 227-254.
15. Bogner RH, Banga AK (1994) Iontophoresis and Phonophoresis. US Pharm19: H10-H26.
16. Pikal MJ (2001) The role of electroosmotic flow in transdermal iontophoresis. Adv Drug Del Rev 46: 281-305.
17. Longsheng H, Bozena B, Kohn M (2010), Iontophoretic Transdermal Drug Delivery, in Handbook of Non-Invasive Drug Delivery Systems:95-118.
18. Mitragotri S (2004) Sonophoresis: a 50-year journey. Drug Discov Today 9: 735-736.
19. Escobar CJJ, Martínez DB, Gonzalez MAV, Cruz IMR, Delgado CLD (2009) The Use of Sonophoresis in the Administration of Drugs Throughout the Skin. J Pharm Pharmaceutal Sci 12: 88-115.
20. Murthy SN (1999) Magnetophoresis: An approach to enhance transdermal drug diffusion. Pharmazie 54:377–384.
21. Nanda A, Nanda S, Khan GNM (2006) Current Developments using emerging Transdermal Technologies in physical enhancement methods. Curr Drug Deliv3: 233-2
22. Murthy NS, Boguda VA, Payasada K (2008) Electret Enhances Transdermal Drug Permeation. Biol Pharm Bull 31: 99.
23. Cui L, Jiang J, Zhang L, Song C, Zhao W, et al. (2001) Enhancing effect of electret on transdermal drug delivery. J electrostatics 51: 153-158 31. Zhongfu C, Zhenzhong CGW (1998) Charge storage and transport in polymethylmethacrylate (PMMA) film. J Electrostat 44: 1-2.
24. Burkoth TL, Belhouse BJ, Hewson G (1999) Transdermal and transmucosal powdered delivery. Crit Rev Ther Drug Carrier Syst 16: 331-384
25. Jones S, Brown MB (2005) Evolution of Transdermal Drug Delivery: Recent progress in active transdermal drug delivery technologies has helped miniature, powerful devices to generate required clinical responses. Pharmaceutical Formulation and Quality 2: 36-41.
26. Long BDJ, Sweeney PA, Burkoth TL, Belhouse BJ (1998) Effects of particle size and cylinder pressure on dermal powerject delivery of testosterone to conscious rabbits. ProcIntSymp Control RelBioact Ma 25: 964.

27. Jacques SL, McAuliffe DJ, Blank IH, Parrish JA (1987) Controlled removal of human stratum corneum by pulsed laser. J Invest Dermatol 88: 88-93.
28. Nelson JS, McCullough JL, Glenn TC, Wright WH, Liaw LHL, et al. (1991) Mid-infrared laser ablation of stratum corneum enhances in vitro percutaneous transport of drugs. J Invest Dermatol 97: 874-879.
29. Nanda S, Anand S, Nanda A (1998) Recent physical methods in transdermal drug delivery research. Indian J Pharm Sci 60: 185.
30. Schrammand J, Mitragotri S (2002) Transdermal drug delivery by jet injectors: energetics of jet formation and penetration. Pharm Res 19: 1673-16766.
31. Cross SE, Roberts MS (2004) Physical enhancement of transdermal drug application: Is delivery technology keeping up with pharmaceutical development? Curr Drug Deliv 1: 81-92.
32. Shivanand P, Binal P, Viral D (2009) Microneedles: Progress in Developing New Technology for Painless Drug Delivery. Int J Pharm Tech Res 1: 1279-1282
33. Prausnitz MR (2004) Microneedles for transdermal drug delivery. Adv Drug Deliv Rev 56: 581-587.
34. Henry S, McAllister DV, Allen MG, Prausnitz MR (1998) Microfabricatedmicroneedles: a novel approach to transdermal drug delivery. J Pharm Sci 87: 922-925.
35. R.JayachandraBabuandLiChen(2015):PyrrolidonesasPenetrationEnhancers,Springer, Berlin Heidelberg, 291-299.
36. Kanikkannn N, R. Jayachandra Babu, Li Chen (2015): Fatty Alcohols, Fatty Acids, and Fatty Acid Esters as Penetration Enhancers, Springer, BerlinHeidelberg,133-150.
37. Bauerova K, Matusova1 D, Kassaf Z (2001): Chemical enhancers for transdermal drug transport, European Journal of Drug Metabolism And Pharmacokinetics,26, No.1(2):85- 94.
38. Roberts MS, Walker M (1993) Pharmaceutical Skin Penetration Enhancement. Marcel Dekker, NY, USA, pp: 1-30.
39. Karande P, Mitragotri S (2009) Enhancement of transdermal drug delivery via synergistic action of chemicals. Biochim Biophys Acta 1788: 2362- 2373
40. Patil UK, Saraogi R (2014): Natural products as potential drug permeation enhancer in transdermal drug delivery system, Archives of Dermatological Research,306:419–426.
41. Chen Y, Shen, Y, Guo X, Zhang C, Yang W, et al. (2006) Transdermal protein delivery by a coadministered peptide identified via phage display, Nat Biotechnology 24:455-460
42. Rothbard JB, Garlington S, Lin Q, Kirschberg T, Kreider E, et al. (2000) Conjugation of arginine oligomers to cyclosporin a facilitates topical delivery and inhibition of inflammation. Nat Med 6: 1253-1257.
43. Daniels R (2004) Strategies for Skin Penetration Enhancement. Skin Care Forum.
44. Pellet M, Raghvan SL, Hadgraft J, Davis A (2003) Transdermal Drug Delivery (2 ndedn.), Marcel Dekker, NY, USA.
45. Higuchi T (1977) Design of Biopharmaceutical properties through Prodrugs and Analogs, Washington DC, USA.
46. Tojo K, Valia KH, Chotani G, Chien YW (1985) Long term permeation kinetics of estradiol: IV A Theoretical approach to simultaneous skin permeation and bioconversion of estradiol esters. Drug DevInd Pharm 11: 1175-1193.