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Recent Techniques for Transdermal Penetration Enhancement

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ABSTRACT: There is considerable interest in the skin as a site of drug application for both local and systemic effect. The transdermal route has numerous advantages over the more traditional drug delivery routes. These include high bioavailability, absence of first pass hepatic metabolism, steady drug plasma concentrations and the fact that therapy is non-invasive. The main obstacle to permit drug molecules is the outermost layer of the skin, the stratum corneum. However, the major limitation of this route is the difficulty of permeation of drug through the skin. Innovative research exploiting penetration-enhancing strategies, such as iontophoresis, electroporation, microneedles, and sonophoresis, holds promise for the successful use of these drugs as consumer-friendly, transdermal dosage forms in clinical practice. This review outlines promising new technologies involved in enhancing transdermal permeation. In this review, we have discussed the physical, chemical, biological and other penetration enhancement technology for transdermal drug delivery as well as the probable mechanisms of action.

KEYWORDS: Anatomy of skin**,** Penetration enhancers, Biological enhancement, chemical enhancement, physical enhancement, transdermal delivery.

I. INTRODUCTION

Transdermal drug delivery system is convenient route for the delivery of drugs having short biological half life. Transdermal drug delivery is based on absorption of drugs into the skin after topical application.Transdermal patches are pharmaceutical preparation of varying sizes containing one or more active ingredients that when applied to skin deliver drug directly into systemic circulation after passing through skin barrier.1 Penetration enhancers are the substances used to increase permeation of skin mucosa. Penetration enhancer increases the absorption of penetrant through the skin which is also known as absorption promoter or absorption enhancers. Penetration enhancers used to increase the permeability of drug through skin. Penetration enhancers are the substances used to increase permeation of skin mucosa. Penetration enhancer increases the absorption of penetrant through the skin which is also known as absorption promoter or absorption enhancers. Penetration enhancers used to increase the permeability of drug through skin.

ANATOMY OF SKIN [1]

Skin is the largest organ of the human body, providing around 10% of the body mass of an average person, and it covers an average area of 1.7 m2. Such a large and easily accessible organ.apparently offers ideal and multiple sites to administer therapeutic agents for both local and systemic actions, human skin is a highly efficient self-repairing barrier designed to keep ‘the insides in and the outside out’. Primary function of skin is protection which covers physical, chemical, micro biological, UV radiation and free radicals. Skin also participates in thermoregulation and vitamin D synthesis Structure of human skin can be categorized in three main layers as shown in figure 1.

- Subcutaneous fat layer (hypodermis)
- Dermis
- Epidermis

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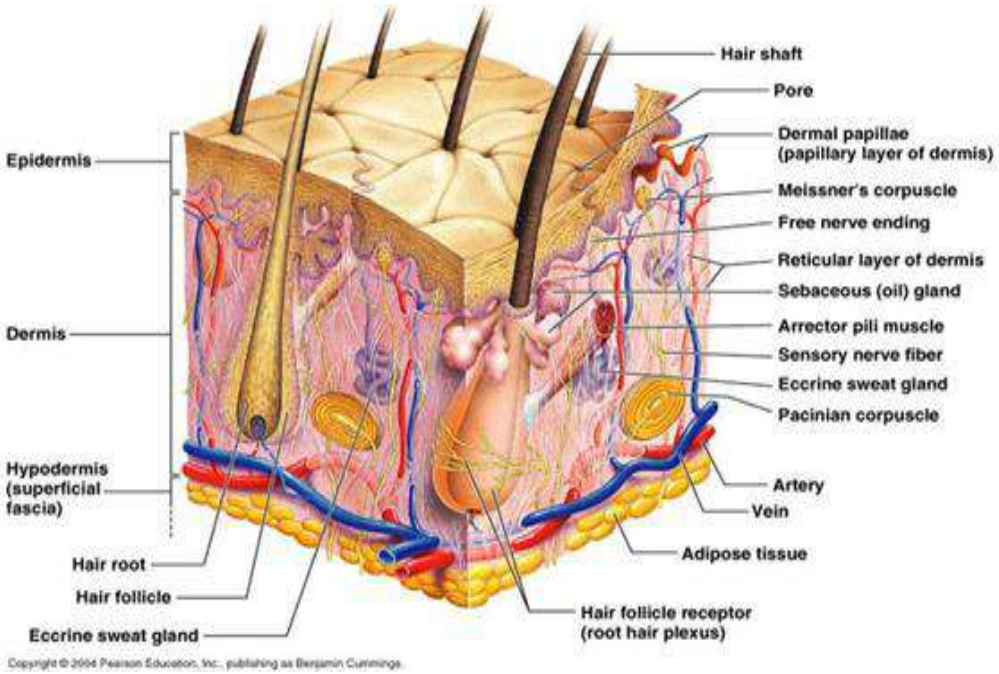

Figure 1: Anatomy of Skin

ROUTES OF PENETRATION

The diffusant has two potential entry routes to the viable tissue, through the epidermis itself or diffusion through shunt pathway mainly hair follicles with their associated sebaceous glands and the sweat ducts as shown in figure 1.

Therefore there are following two major routes of penetration.

Transcorneal Penetration

- Intra Cellular Penetration
- Intercellular Penetration

Ideal Properties of Penetration Enhancers [2]

1. These materials should be non toxic, non irritating, pharmacologically inert, non allergic.
2. It should be compatible with drug and excipients.
3. It should have no pharmacological activity within body.
4. It should be cosmetically acceptable.
5. It should be odorless, tasteless, colorless and in expensive and have good solvent properties.
6. It should be chemically and physically stable.
7. Duration of action should be both predictable and reproducible and work rapidly.
8. It should be tested in research laboratories.

Uses of Penetration Enhancers [3, 4]

1. It is used to increase the delivery of ionizable drugs. Example: timolol maleate etc.
2. To deliver the impermeable drugs. Example: heparin etc.
3. To maintain level in blood.
4. To improve the efficacy of less potent drugs with higher dose.
   Example: oxymorphane.
5. To deliver the drugs having high molecular weight like peptide and hormones.
6. To decrease lag time of transdermal drug delivery system.

Merits of Penetration Enhancers [5]

1. Most drugs penetrate at rates sufficiently high for therapeutic efficiency by using penetration enhancers.
2. It is useful for unabsorbable drugs to facilitate their absorption through skin.
3. It can improve transdermal absorption of topical preparation.
4. They having no adverse effect on skin.
5. These may be non toxic materials.
6. These do not affect zero order skin permeation profile of skin.
7. The terpenes like limonene in propylene glycol solution are effective penetration enhancer for cytotoxic drugs.
8. It also acts as rate limiting factor.

Demerits of Penetration Enhancers [6]

1. The effective concentration varies from drug to drug.

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2. The uses of different penetration enhancer with various concentrations are restricted completely.
3. Physicochemical properties of enhancers are also affecting the side effects in the body.

Pathway of Transdermal Permeation [5]
Permeation occur by diffusion via
1. Transdermal permeation through the stratum corneum.
2. Intercellular permeation through stratum corneum.
3. Transappendaged permeation via hair follicle, sebaceous and sweat glands.

MECHANISM OF ACTION OF PENETRATION ENHANCERS [3,4]

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.

TABLE 1: CLASSIFICATION OF PENETRATION ENHANCERS AND TECHNIQUES

Types/Techniques of penetration enhancers	Mechanism of action	Examples
1. Chemical enhancers	They act by three mechanisms[10] 1. By distruption of highly ordered structure of stratum corneum lipid. 2. By interaction with intercellular protein. 3. By improved partition of the drug or solvent into stratum corneum.	1. Sulphoxides and similar chemicals-dimethyl sulphoxide(DMSO),dimethyl formamide(DMF),dimethyl acetamide(DMAC) 2. Azones 3. Pyrrolidones 4. Fattyacids–Lauric acid, Myristic acid and capric acid 5. oxizolidinones (4-decycloxazolidine-2-one) 6. Amine and Amides –Urea 7. Surfaceactiveagents–sodium lauryl sulphate, Benzalkonium chloride 8. cyclodextrins
2. Drug Vehicle Based	Interaction of enhancers with stratum corneum and development of SAR for enhances with optimal characteristics and minimal toxicity[11]	Ion pairs and complex Coacervates chemical potential adjustment
3. Natural Penetration enhancers	Mechanism for Terpenes It may increase one or more of following Effects9 1. Partition coefficient 2. Diffusion coefficient 3. Lipid Extraction 4. Drug Solubility 5. Macroscopic Barrier Perturbation 6. MolecularOrientation of Terpenes Molecule with Lipid Bilayer	1. Terpens-Menthol, Linalool, Limonene, Carvacrol. 2. Essential oil-Basil oil, Neem oil, Eucalyptus, Chenopodium, Ylang- Ylang.

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4. Physical Enhancers	These are variable techniques available for increasing the penetration by physical separation and magnetic and ultrasonic.	1. Iontophoresis 2. Sonophoresis 3. Phonophoresis 4. Magnetophoresis 5. Electroporation 6. Thermophoresis 7. Radiofrequency 8. Needleless injection 9. Hydration of stratum corneum 10. Stripping of stratum corneum
5. Biochemical Approach	They act by modifying substances by converting it in to suitable form.	1. Synthesis of bio-convertible pro drugs 2. co-administration of skin metabolite Inhibitors
6. Miscellaneous Enhancers	Having Various Mechanism	1. Lipid synthesis inhibitors 2. Phospholipids 3. Clofibric acid 4. Dodecyl –N,N-Dimethyl

CHEMICAL ENHANCERS:

1. SULPHOXIDES AND SIMILAR CHEMICALS

It is one of earliest and most widely used penetration enhancer. Since DMSO is problematic for use, researchers investigated similar chemically related material as enhancers DMAC (Dimethyl acetamide), DMF (Dimethyl formamide). Mechanism of Sulphoxide Penetration enhancer ar widely used to denature protein and on application to human skin has been shown to change the intercellular keratin configuration, from helical to beta sheet DMF irreversibly damages human skin membrane but has been found in vivo to promote the bioavailability of betamethasone-17-benzoate as measured by vasoconstrictor assay. [11]

2. AZONES

It is highly lipophilic material. It enhances skin transport of variety of drugs including steroids, antibiotic and antiviral agents. It is effective at low concentration between 0.1-5% but more ofte between 1- 3%. Azone molecules may exist dispersed within the barrier lipoid or separate domains within the Bilayer 11. When Azone was used in combination with PG, the flux of methotrexate and Piroxicam increased significantly. Azone is the most effective penetration enhancer for low molecular weight heparin across human skin as compared with terpenes. The order of enhancing power of enhancers laurocapram > nerolidol>eucalyptol. [10]

3. PYRROLIDONES

It is used to generate reservoirs within skin membrane. Such a reservoir effect offers a potential for sustained release of a permeant from the stratum corneum over extended time periods. N-Methyl-2- Pyrrolidone (NMP) widely used to enhance skin absorption of many drugs example insulin and ibuprofen and Flurbiprofen. NMP enhanced permeation of anti-inflammatory drugs like ketoprofen.2-Pyrrolidone and NMP were assessed in enhancing topical bioavailability of betamethasone- 17-benzoate using Dimethylisosorbide (DMI) as standard solvent.2-Pyrrolidone enhances Transdermal permeation of caffeine.[11]

4. FATTY ACIDS AND ESTERS

It has been seen that unsaturated fatty acids are more effective than saturated fatty acids. Fatty acids having greater enhancing effect on lipophilic drugs. Oleic acid is mono-unsaturated fatty acid increase the permeation of lipophilic drugs through skin and buccal mucosa by transdermal cellular pathway. It is an effective enhancer for Piroxicam.11 Lauric acid used in propylene glycol enhanced the delivery of highly lipophilic antiestrogen [11]. It increases flux of many drugs examples are salicylic acid 28 folds and 5- flurouracil flux 56 folds. Myristic acid in combination PG increased permeation of Oxymorphane. In organophosphate poisoning, a patch of Propionic acid and Oleic acid produced greater transdermal delivery of Physostigmine than Propionic acid alone. [12]

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5. OXAZOLIDINONES

Oxazolidinones have ability to localize coadministrated drug in skin layer. The structural features are related to sphingosine and ceramide lipids which are naturally found in upper skin layers11. Oxazolidinones such as 4-decyloxazolidin-2-one has been reported to localize the delivery of many active ingredients such as retinoic acid in skin layer. [13]

6. AMINES AND AMIDES

Cyclic Urea is biodegradable and non toxic molecule. Enhancement occurs by both hydrophilic activity and lipid disruption. Urea used as hydrating agent in dermatology for the treatment of neurodermatitis andother hyperkeratotic skin conditions. [11]

7. SURFACE ACTIVE AGENTS

Surface active agents are added to formulation 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. [11]

Three types of surface active agents are [14]

- Cationic surfactant- Benzalkonium chloride,
- Cetyltrimethyl Ammonium bromide.
- Nonionic surfactant- dodecyl betaine.
- Anionic surfactant- Sodium lauryl sulphate.

Function of Anionic and Cationic surfactant are they swell the stratum corneum and interact with intercellular keratin. Surfactants are low to moderate molecular weight compounds which contain one hydrophobic part, which is readily soluble in oil but sparingly soluble or insoluble in water, and one hydrophilic part, which is sparingly soluble or insoluble in oil but readily soluble in water.

8. CYCLODEXTRINS

These compounds form complexes with lipophilic drugs. Alone are less effective as penetration enhancer than combined with fatty acid and propylene glycol. [11]

DRUG VEHICLE BASED

It is based on drug selection, eutectic system, vesicles, particles, Prodrug and chemical potential of drug.

1. Ion pairs and Complex Coacervates

It involves adding of oppositely charged species to a charged drug, formation of an ion pair in which charges are neutralized so that complex can partition into and permeate through the stratum corneum. [15]

2. Drug selection

Drug should be selected as it fits in criteria of transdermal delivery. Prodrug approach enhances the drug permeation through skin. There are certain criteria of drug selection as [16]

_ Aqueous solubility > 1mg/ml
_ Lipophillicity 10<ko/w<1000
_ Molecular weight <500 Daltons
_ PH of aqueous saturated solution-5-9
_ Dose deliverable <10mg/day

NATURAL PENETRATION ENHANCERS

Essential oils, Terpenes and Terpenoids [17]

Chemical structure of Terpenes and Terpenoids consist of number of repeated isoprene (C5H8) units which is used to classify terpenes.

- Monoterpenes - have two isoprene units.
- Sesquiterpenes –have three isoprene units.
- Diterpenes-have four isoprene units.

Terpenes and Terpenoids are constituted of volatile oil.

Terpenes are compounds comprising of only Carbon, Hydrogen and Oxygen alone. Eucalyptus, Chenopodium, Ylang-Ylang are effective penetration enhancers for 5-flouorouracil.

1. Cineole-It is Monoterpenoid. It is also known as1,8-Cineol, 1, 8-cineole, Limonene oxide, Cajeputol, 1, 8- epoxy-p-methane, 1,8-oxido-p-me-thane, eucalyptol etc. It is used in suppository form for the treatment of respiratory ailments. It is also used as flavoring agent. It is used in Cosmetic, Mouthwash and Cough suppressant.

2. Eugenol-It is slightly soluble in water and soluble in organic solvents. It is a member of ally benzene class of chemical compounds. It is extracted from essential oils especially from nutmeg, clove oil, cinnamon and bay leaf. It reduces the ability to feel and react to painful stimulation.

3. D-Limonene-It is extracted from rinds of citrus fruits. It has two grades which are called food grade and technical grade.

4. Menthol-It is used in antipruritic creams and as an upper respiratory tract decongestant. It is

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obtained from flowering tops of Mentha piperita. It is used as an enhancer for transdermal delivery of variety of drugs including caffeine, hydrocortisone, and Propranolol hydrochloride.

PHYSICAL ENHANCERS [18]

There are numerous physical methods are used for penetration enhancers.

1. Iontophoresis

It was developed to facilitate the delivery of ionized solute, with inherently low partition coefficients due to their charged states, across tissue membranes. The techniques involves the application of a small electric current to a drug reservoir on the surface of the skin, with the same charged electrode as the solute of interest placed together to produce a repulsion effect that effectively drives the solute molecules away from the electrode and in to skin.

2. Sonophoresis

It is the application of ultrasound to enhance the percutaneous drug delivery. The effect of ultrasound on tissue is either thermal or non thermal with the non thermal cavitations effect thought to be the most important in its application to drug delivery.

3. Magnetophoresis

It Consist of magnetic nanoparticles wrapped by a phospholipids Bilayer which can be applied for drug delivery systems. It acts as an external driving force to enhance drug delivery across the skin.

4. Thermal energy

Thermal energy when applied to skin, cause increased skin permeability. Heating during topical application of a drug dilates penetration pathway in the skin and increase kinetic energy and movement of particles in the treated area which facilitates drug absorption.

5. Electoporation

It involves the application of short, high voltage pulses to skin. The Mechanism by formation of transient pores due to electric pulses that subsequently allow the passage of Macromolecule from outside of the cell to the intracellular space.

6. Hydration of stratum, corneum

Permeability varies according to skin condition. Hydrated skin is more permeable than dry skin. Hydration of skin reduces resistance by loosening the packaging of layers of stratum corneum.

MISCELLANEOUS ENHANCERS [13]

1. Clofibric Acid

The best enhancement of hydrocortisone-21 acetate and betamethasone-17-valerate was observed with Clofibric acid octyl amide when applied 1 hr prior to each steroid. Amide analogues are generally more effective than ester derivatives of the same carbon chain length.

2. Phospholipids

Phosphatidyl Choline derivatives promoted the percutaneous penetration of erythromycin. Six phosphatidyl glycerol derivatives (PGE [from egg yolk], PGS [from soyabean], dimyristyl phosphatidyl glycerol [DMPG], dipalmityl phosphatidyl glycerol [DPPG], distearyl phosphatidyl glycerol [DSPG], dioleyl phosphatidyl glycerol [DOPG] derivatives); five phosphatidyl Choline (PC) derivatives (PCS [from soyabean], PCE [from egg yolk], dioleyl PC [DOPC], dilinoleoyl PC [DLPC], hydrogenated PC [HPC]); and two phosphatidyl ethanolamine derivatives were studied using indomethacin.

3. Lipid synthesis inhibitors

It enhances the delivery of some drugs like Lidocaine and caffeine Fatty acid synthesis inhibitors like 5- (tetradecyloxy)-2-furancarboxylic acid (TOFA) and the cholesterol synthesis inhibitors fluvastatin (FLU) or cholesterol sulfate (CS) delay the recovery of barrier damage produced by prior application of penetration enhancers like DMSO, acetone, and the like.

NOVEL PENETRATION ENHANCERS

Numerous class of novel compounds have been evaluated for penetration enhancement activity,including soft enhancement for percutaneous absorption (SEPA), for example, 2 N-nonyl-1,3- dioxolanes, N-acetyle prolinate esters (such as pentyland octyl-N-acetyle prolinate), alkyldiloxanes (e.g.,1- Alkyl-3-b-Dglucopyranosyl-1,1,3,3-tetramethyl disiloxanes), transcarbam(such as 5 (dodecyloxycarbonyl)pentylammonium-5-(dodecyloxycarbonyl)pentylcarbamate),iminosulfurane (like N-hexyl,N-benzoyl-S,S-dimethyliminosulfuranes), capsaicin derivatives (e.g., Nonivamide), cinnamene compounds (such as cinnamic acid, Cinnamaldehyde etc), terpenes (like

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clove and basil oil) and synergistic combination of penetration enhancers (SCOPE). [19]

EXAMPLES OF NOVEL NATURAL PENETRATION ENHANCERS:

1. BASIL OIL

It is the natural penetration enhancer. It is used to enhance the permeability of drug across the skin. It is used as Antibacterial, Antioxidant, and Diuretic. Mechanism act by extraction of lipids from stratum corneum as well as by loosening the H-bonds between ceramide subsequently leading to fluidization of lipid layer. [20]

Research Studies

These articles were cited that Basil oil used as skin penetration enhancer for transdermal delivery of Labetolol Hydrochloride. Basil oil is used as a potential enhancer with reference to Camphor, Geraniol, Thymol and Clove oil. It concludes that Basil oil produced the maximum enhancement over neat vehicle among all enhancers. Activation energies for Labetolol Hydrochloride Permeation in water, Vehicle per se and in presence of 5% w/v Basil oil were found to be 23.16,18.71,10.98 kcal/mole respectively. Lowering of activation energies in presence of Basil oil suggest creation of new polar pathways in skin for enhanced permeation of Labetolol Hydrochloride. [21] Basil oil used for the improvement in bioavailability of transdermally applied Flurbiprofen. It concludes that bioavailability of transdermal Flurbiprofen using basil oil with reference to orally administered Flurbiprofen in albino rats is found to increased by 2.97,3.80 and 5.56 times. [22] Basil oil used to develop transdermal gel of naproxen containing Basil oil as a natural penetration enhancer for improved penetration of Naproxen.

2. CLOVE OIL

It is a natural penetration enhancer. It is used to enhance the permeability of drug across the skin. It is used safely in food, beverages, and toothpaste. It is also used as Antiseptic and Analgesic.

Research Studies

These articles were cited that Evaluated skin permeation effect of clove oil in rabbits and compare in vitro absorption and in vivo permeation using ibuprofen. It concludes that after using Clove oil the permeation rate enhanced was 7.3. [22]

Clove oil used as penetration enhancer in formulation and evaluation of ant arthritic herbal preparation (ointment). [23]

3. CAPSAICIN

It is used as penetration enhancer to increase the permeability of drug across the skin. Topical Capsaicin formulations are used for pain management. Mechanism- several mechanism are involved. These include receptor inactivation, block of voltage activated calcium channels, intracellular accumulation of ions leading to osmotic changes and activation of proteolytic enzymes processes. Systemic and Topical capsaicin produces a reversible antinociceptive and anti-inflammatory action after an initial undesirable algesic effect. Capsaicin analogues, such as olvanil, have similar properties with minimal initial pungency.

Systemic capsaicin produces antinociception by activating capsaicin receptors on afferent nerve terminals in the spinal cord. Spinal neurotransmission is subsequently blocked by a prolonged inactivation of sensory neurotransmitter release. Local or topical application of capsaicin blocks C-fiber conduction and inactivates neuropeptide release from peripheral nerve endings. These mechanisms account for localized antinociception and the reduction of neurogenic inflammation respectively. [24]

RESEARCH STUDIES

These articles were cited that In vitro study was conducted to investigate the changes of indomethacin transdermal permeation pretreated by Capsaicin and Nonivamide, two compounds chemically similar to Azone. Both enhanced the Flux of indomethacin across nude mouse skin. Better effect was obtained by the combination with capsaicin than Nonivamide. Investigate the penetration properties of naproxen and the enhancer activity of capsaicin. The effect of capsaicin was compared with well known enhancer Azone; Different amounts of chosen enhancers were applied to the skin surface before the experiment.

Commercially available naproxen gel formulation and an alternative formulation containing 3 % capsaicin were also studied and results were compared. Penetrations were found to be increased when the skin was treated with Azone and capsaicin. It was found that capsaicin caused some alterations on stratum corneum layer of the skin like Azone therefore it was observed that

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capsaicin caused an enhanced penetration of naproxen through human skin. It concludes that capsaicin was found to be a quite capable enhancer for skin penetration of drugs like the well-known enhancer, Azone. [25] A high concentration Capsaicin 8% patch was recently approved in the EU and USA.A single 60 min application in patients with neuropathic pain produced effective pain relief for up to 12 weeks. Advantages of using capsaicin patch include patient compliances, longer duration of action. Mechanism of action of patch of capsaicin has been ascribed to depletion of Substance P. Topical capsaicin acts in the skin to attenuate cutaneous hypersensitivity and reduce pain by a process as Defunctionalization of nociceptor fibers. It suggests that the utility of Topical capsaicin may extend beyond peripheral neuropathies. [26]

EXAMPLES OF NOVEL SYNTHETIC PENETRATION ENHANCERS :

1. Cinnamene Compounds

Research Studies

This article was cited that the Cinnamene compounds, cinnamic acid, Cinnamaldehyde and cinnamic alcohol were used as penetration enhancers for transdermal delivery of the ligustrazine hydrochloride. The effects and mechanism of penetration promotes on the in vitro percutaneous absorption of ligustrazine hydrochloride through porcine dorsal skin. It concludes that the penetration of ligustrazine hydrochloride by cinnamic acid was the greatest. [27]

II. CONCLUSION

Skin penetration enhancers are rapidly using technique for the permeation of drugs through the skin by transdermal drug delivery system. Penetration enhancers plays critical role in development of patches. As it was seen in different articles that it improves the bioavailability and efficacy of drugs. It helps in achieving therapeutic dose of drug through the skin. 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.

Skin penetration enhancement techniques have been developed to improve bioavailability and increase the range of drugs for which topical and transdermal delivery is a viable option. The noninvasive route of delivery systems has many advantages over the conventional delivery systems. The permeation of drugs through skin can be enhanced by various physical methods & it becomes challenging aspect in research work.

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