USE OF NOVEL PENETRATION ENHANCERS AND TECHNIQUES IN TDDS

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ABSTRACT

Transdermal route is the most convenient route for the delivery of drug having short biological half life and poorly soluble drugs. This route provides many advantages over other routes as avoiding first pass hepatic metabolism, decrease side effects, GI effects and increased bioavailability. Human skin is remarkably efficient barrier, designed to keep “our insides in and outsides out”. This barrier property causes difficulties for transdermal delivery of therapeutic agents. One long standing approach to increase the range of the drugs that can be effectively delivered via this route has been to use penetration enhancers, chemicals that interact with skin constituents to promote drug flux for both local and systemic effect. Skin penetration enhancement techniques have been developed to improve bioavailability and to increase the range of drugs for which topical and transdermal delivery is viable option. The penetration of the drug through skin can be enhanced by both chemical penetration enhancement and physical methods. In this review, we have discussed the physical and chemical penetration enhancement technology for transdermal drug delivery as well as the probable mechanism of action. To-date, a vast array of chemicals and techniques has been evaluated as penetration enhancers, yet their inclusion into topical or transdermal formulations are limited since the underlying mechanisms of action of these agents are seldom clearly defined. In this article we review some uses of the more widely investigated chemical penetration enhancers and discuss possible mechanisms of action.

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INTRODUCTION

Transdermal drug delivery system (TDDS) provides a means to sustain drug release as well as reduce the intensity of action and thus reduce the side effects linked with its oral therapy. Transdermal drugs are self-contained, discrete dosage form. Transdermal patch (Skin patch) uses a special membrane to control the rate at which the liquid drug contained in the reservoir within the patch can pass through the skin and into the bloodstream. Some drugs must be combined with substances, such as alcohol, that increase their ability to penetrate the skin in order to be used in a skin patch. The all-inclusive transdermal patch market approaches £2 billion, based on only ten drugs including scopolamine, nitroglycerine, clonidine, estrogen, testosterone, fentanyl, and nicotine, with a lidocaine patch soon to be marketed¹. Drugs administered through skin patches include scopolamine (for motion sickness), nicotine (for quitting smoking), estrogen (for menopause and to prevent osteoporosis after menopause), nitroglycerin (for angina), and lidocaine to relieve the pain of shingles (herpes zoster). Molecules of insulin and many other substances, however, are too large to pass through the skin. Patches applied to the skin eliminate the need for vascular access by syringe or the use of pumps. Transdermal patches were developed in the 1970s and the first was approved by the FDA in 1979 for the treatment of motion sickness. It was a three-day patch that delivered scopolamine Today there exist a number of patches for drugs such as clonidine, fentanyl, lidocaine, nicotine, nitroglycerin, oestradiol, oxybutinin, Scopolamine and testosterone. There are also combination patches for contraception, as well as hormone replacement. Depending on the drug, the patches generally last from one to seven days.

The major advantages provided by transdermal drug delivery include the following: improved bioavailability, more uniform plasma levels, longer duration of action resulting in a reduction in dosing frequency, reduced side effects and improved therapy due to maintenance of plasma levels up to the end of the dosing interval compared to a decline in plasma levels with conventional oral dosage forms. Transdermal patches have been useful in developing new applications for existing therapeutics and for reducing first-pass drug-degradation effects. Patches can also reduce side effects; for example, oestriadiol patches are used by more than a million patients annually and, in contrast to oral formulations, do not cause liver damage. Of two major sub-categories - therapeutic and cosmetic), aroma patches; weight loss patches, and non medicated patch markets include thermal and cold patches, nutrient patches, skin care patches (a category that consists patches that measure sunlight exposure²).

Advantages:
- Topical patches are a painless, noninvasive way to deliver substances directly into the body.
- Topical patches are a better way to deliver substances that are broken-down the stomach acids, not well-absorbed from the gut, or extensively degraded by the liver. And also avoids first pass metabolism.
- Topical patches over a controlled, steady delivery of medication over long periods of time.
- Topical patches have fewer side effects than oral medication or supplements.
- Topical patches are easier to use and remember.
- Topical patches over an alternative to people who cannot, or prefer not to take medications or supplements orally.
- Topical patches are cost-effective.
- People prefer topical patches³.

Limitation:
- Transdermal drug delivery system cannot deliver ionic drugs.
- Transdermal drug delivery system cannot achieve high drug levels in blood/plasma.
- It cannot develop for drugs of large molecular size.
- Transdermal drug delivery system cannot deliver drugs in a pulsatile fashion.
- Transdermal drug delivery system cannot develop if drug or formulation causes irritation to skin.
- Limitation of Transdermal drug delivery system can be overcome to some extent by novel approaches such as Iontophoresis, electroporation and ultrasound⁴.

Drug Formulation Based Enhancement Approaches:
Ideal Properties of Penetration Enhancers
1. These materials should be non toxic, non irritating, pharmacologically inert, non allergic.
2. There should not be any kind of interaction of penetration enhancer with drug and excipient.
3. It should have no pharmacological activity within body.
4. It should be well accepted cosmetically.
5. It should be odorless, tasteless, colorless and inexpensive 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
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: oxymorphone.
5. To deliver the drugs having high molecular weight like peptide and hormones.
6. To decrease lag time of transdermal drug delivery system.

The method employed for modifying the barrier properties of the stratum corneum to improve drug penetration and absorption through skin may be classified into the following categories:
1. Chemical enhancement
2. Physical enhancement
3. Biochemical enhancement
4. Super saturation enhancement
5. Bioconvertable prodrug

MECHANISM OF ACTION OF PENETRATION ENHANCERS

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 at 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 diffusion resistance and increasing the permeability. Some penetration enhancers cause change in the protein conformation.

Physical Enhancement:

Iontophoresis

Iontophoresis passes a few mill amperes of current to a few square centimeters of skin through the electrode placed in contact with the formulation, which facilitates drug delivery across the barrier. Iontophoresis enhances drug delivery across the skin by two principal mechanisms: Electrorepulsion and electroosmosis. Electrorepulsion is the direct effect of the applied electric field on a charged permanent. The second mechanism, electroosmosis, results from the fact that the skin supports a net negative charge at physiological pH. Iontophoresis is a non invasive method used to boost high concentration of a charged substance, generally medication or bioactive agents, transdermally by repulsive electromotive force using a small electrical current applied to an Iontophoresis chamber containing a similarly charged active agent and its vehicle. These movements are measured in units of chemical flux, commonly μmol/cm² h. This technique is based on the general principle that like charges repel each other. Thus, during Iontophoresis, if delivery of a positively charged drug (D⁺) is desired, the charged drug is dissolved in the electrolyte surrounding the electrode of similar polarity, i.e. the anode in this example. Mainly used for pilocarpine delivery to induce sweating as part of cystic fibrosis diagnostic test. Iontophoretic delivery of lidocaine appears to be a promising approach for rapid onset of anesthesia.
Electroporation
Electroporation is a method of application of short, high-voltage electrical pulses to the skin. After electroporation, the permeability of the skin for diffusion of drugs is increased by 4 orders of magnitude. The electrical pulses are believed to form transient aqueous pores in the stratum corneum, through which drug transport occurs. It is safe and the electrical pulses can be administered painlessly using closely spaced electrodes to constrain the electric field within the nerve-free stratum corneum.

Application by ultrasound
Application of ultrasound, particularly low frequency ultrasound, has been shown to enhance transdermal transport of various drugs including macromolecules. It is also known as sonophoresis. Katz et al. reported on the use of low-frequency sonophoresis for topical delivery of EMLA cream.

Use of microscopic projection
Transdermal patches with microscopic projections called microneedles were used to facilitate transdermal drug transport. Needles ranging from approximately 10-100 μm in length are arranged in arrays. When pressed into the skin, the arrays make microscopic punctures that are large enough to deliver macromolecules, but small enough that the patient does not feel the penetration or pain. The drug is surface coated on the microneedles to aid in rapid absorption. They are used in development of cutaneous vaccines for tetanus and influenza.

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.

Thermal energy
Thermal energy when applied to skin causes 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.
Chemical Enhancement:

Ideal characteristics of chemical penetration enhancers:

Ideally, penetration enhancers reversibly reduce the barrier resistance of the stratum corneum without damaging viable cells. Some of the more desirable properties for penetration enhancers acting within the skin have been given as:\(^5,^6\):

- They should be non-toxic, non-irritating and non-allergenic
- They would ideally work rapidly; the activity and duration of effect should be both predictable and reproducible
- They should have no pharmacological activity within the body.
- The penetration enhancers should work unidirectionally, i.e., they should allow therapeutic agents into the body while preventing the loss of endogenous materials from the body.
- When removed from the skin, barrier properties should return both rapidly and fully to normal.
- They should be cosmetically acceptable with an appropriate skin feel.

Not surprisingly, no such material that possesses the above ideal properties has yet been discovered although some chemicals demonstrate several of the above attributes.

Mechanism of chemical penetration enhancement:

Penetration enhancers may act by one or more of three main mechanisms:\(^5\):

1. Disturbance in the highly ordered structure of stratum corneum lipid.
2. Interaction with intercellular protein.
3. Improved partition of the drug, co enhancer or solvent into the stratum corneum.

Sulphoxides and similar chemicals

Dimethyl sulphoxides (DMSO) is one of the earliest and most broadly studied penetration enhancers. It is a dominant aprotic solvent which hydrogen bonds with itself rather than with water. It is colorless, odourless and is hygroscopic and is often used in many areas of pharmaceutical sciences as a “universal solvent”. DMSO alone has been applied topically to treat systemic inflammation. DMSO works rapidly as a penetration enhancer - spillage of the material onto the skin can be tested in the mouth within a second. Even though DMSO is an excellent accelerant, it does create problems. The effect of the enhancer is concentration-dependent and generally cosolvent containing > 60% DMSO are needed for optimum enhancement efficacy. However, at these relative high concentrations, DMSO can cause erythema and wheal of the stratum corneum. Denaturing of some skin proteins results in erythema, scaling, contact urticaria, stinging and burning sensation\(^2,^11\).

Azone

Azone (1-dodecylazacycloheptan-2-one or laurocapran) was the initial molecule purposely designed as a skin penetration enhancer. Azone is a colourless, odourless liquid with a melting point of \(-7 ^\circ C\) and it possesses a smooth, oily but yet non-greasy feel. Azone is a highly lipophilic material with a log \(p\) octanol / water of around 6.2 and it is soluble in and compatible with most organic solvents including alcohol and propylene glycol. Azone enhances the skin transport of a wide variety of drugs including steroids, antibiotics and antiviral agents. Azone is most effective at low concentrations being employed typically between 0.1 - 5% but more often between 1- 3% \(^13\). Azone partitions into a bilayer lipid to disrupt their packing arrangement but integration into the lipid is unlikely to be homogeneous. Azone molecules may exist dispersed within the barrier lipoid or separate domains within the bilayer\(^2,^10\).

Pyrrolidones

Pyrrolidones have been used as permeation enhancers for numerous molecules including hydrophilic (e.g. mannitol and 5-fluouracil) and lipophilic (progesterone and hydrocortisone) permeants. N-methyl-2-Pyrrolidone was employed with limited success as a penetration enhancer for captopril when formulated in a matrix-type transdermal patch. The pyrrolidones partition well into human stratum corneum within the tissue and they may act by altering the solvent nature of the membrane. Pyrrolidones have been used to generate reservoirs within the skin membrane. Such a reservoir effect offers a potential for sustained release of a permeant from the stratum corumand over extended time periods\(^2,^11,^12\).

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 and other hyperkeratosis skin conditions.

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.\(^9\)

Three types of surface active agents are 12 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.
CYCLODEXTRINS

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

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.\textsuperscript{13}

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\textsuperscript{14}

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

Fatty acids

Percutaneous drug absorption has been increased by a wide variety of long-chain fatty acids, the most popular of which is oleic acid. It is of interest to note that many penetration enhancers such as Azone contain saturated or unsaturated hydrocarbon chains and some structure - activity relationships have been drawn from the extensive studies of Amongst who employed a range of fatty acids, acids, alcohols, sulphoxides, surfactants and amides as enhancers for naloxone. Shin et al\textsuperscript{19} studied various penetration enhancers like glycols (diethylene glycol and tetraethylene glycol), fatty acids (lauric acid, myristic acid and capric acid) and nonic surfactant (polyoxyethylene-2-oleyl ether, polyoxyethylene-2-stearly ether) on the release of triprolidine. Lauric acid in Propylene glycol enhanced the delivery of highly lipophilic antiestrogen. Oleic acid greatly increased the flux of many drugs such as increasing the flux of salicylic acid 28-fold and 5-fluorouracil flux 56-fold through human skin membrane \textit{in vitro}. The enhancer interacts with and modifies the lipid domains of the stratum corneum as would be expected for a long chain fatty acid with cis- configuration\textsuperscript{2,14,15}.

Oxazolidinones

Oxazolidinones are a new class of chemical agents which have the potential for use in many cosmetic and personal care product formulations. This is due to their ability to localize co-administered drug in skin layers, resulting in low systemic permeation. The structural features of these permeation enhancers are closely related to sphingosine and ceramide lipids which are naturally found in the upper skin layers. Oxazolidinones such as 4-decyloxazolidin-2-one has been reported to localize the delivery of many active ingredients such as retinoic acid and diclofenac sodium in skin layers. This compound has a higher molecular weight and lipophilicity than other solvent-type enhancers, physical characteristics that may be beneficial in terms of a reduction in local toxicity because of the lack of effective absorption of these enhancers into the lower skin layers where irritation is likely to be occur\textsuperscript{16,17}.

Biological Enhancement:

Biological enhancement transdermal drug delivery system can be achieved by disrupting the final cell and tissue differentiation process that occur in the epidermis. This process is critical to the body’s ability to develop an efficient barrier against exogenous substances. One of the key processes is the formation of intercellular lipid within stratum lucidum and SC layer. The ordered nature of these intercellular lipids is the primary factor that restricts drug permeation across the skin. These lipids are synthesized in situ in stratum basale stratum spinosum and stratum granulosum where they can be viewed as lamellar bodies. The lipid present in these LB include sphingomyelins glucosylceramides phospholipids and cholesterol sulphate, however the lipid found in the intercellular regions of the SC comprise largely of cholesterol free fatty acids and ceramides. Glucosylceramides are converted into ceramides with the aid of Bglucocerebrosidase; the failure to form ceramides from glucosylceramide result in severe barrier abnormality and delayed barrier recovery after acute perturbations.

NATURAL PENETRATION ENHANCERS\textsuperscript{18}:

Essential oils, Terpenes and Terpenoids\textsuperscript{15} Chemical structure of Terpenes and Terpenoids Consist of number of repeated isoprene (C5H8) units which is used to classify terpenes. Monoterpines - 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-fluorouracil.
Cineole-
It is a Monoterpenoid. It is also known as 1, 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 a flavoring agent.
It is used in Cosmetics, Mouthwash and Cough suppressant.

Eugenol-
It is slightly soluble in water and soluble in organic solvents. It is a member of the 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.

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

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

MISCELLANEOUS ENHANCERS

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

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], dipalmitoyl phosphatidyl glycerol [DPPG], distearoyl phosphatidyl glycerol [DSPG], dioleoyl phosphatidyl glycerol [DOPG] derivatives); five phosphatidyl Choline (PC) derivatives (PCS [from soyabean], PCE [from egg yolk], dioleyl PC [DOPC], distearyl PC [DLPC], hydrogenated PC [HPC]); and two phosphatidyl ethanolamine derivatives were studied using indomethacin.

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-acetyl proline esters (such as pentyl and octyl-N-acetyl proline), alkylidioxolanes (e.g., 1- Alkyl – 3 – b – DGlucopyranosyl - 1, 1, 3, 3 - tetramethyl disiloxanes), transcarbam (such as 5- (dodecylxycarbonyl) pentylammonium - 5 (dodecylxycarbonyl) pentylcarbamate), iminosulfuranes (like N - hexyl, N - benzoyl - S, S - dimethy liminosulfuranes), capsaicin derivatives (e.g., Nonivamide), cinnamene compounds (such as cinnamic acid, Cinnamaldehyde etc), terpenes (like clove and basil oil) and synergistic combination of penetration enhancers.

EXAMPLES OF NOVEL NATURAL PENETRATION ENHANCERS
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.
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/w 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.18 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.19 Basil oil used to develop transdermal gel of naproxen containing Basil oil as a natural penetration enhancer for improved penetration of Naproxen.

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 7.3.19 Clove oil used as penetration enhancer in formulation and evaluation of antiarhritic herbal preparation (ointment).20

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 photolytic enzymes processes. Systemic and Topical capsaicin produces a reversible antinociceptive and Anti-inflammatory action after an initial undesirable analgesic 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.21

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 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.22 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 compliance, 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 peripheralneuropathies.22

CONCLUSION

Transdermal drug delivery has enormous potential as a means of delivering drugs that cannot be administered via the oral route, if the inherent weakness can be properly restricted. It is necessary to temporarily reduce the barrier properties of the skin in order to ensure that a clinically efficacious dose can be delivered. 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. Apart from physical and chemical penetration enhancers, novel natural penetration enhancers are being researched for their penetration ability. Thus successful transdermal drug delivery system relies on techniques, such as manipulating drug formulation, drug modification, chemical enhancement and biological enhancement or a combination thereof.
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