Penetration Enhancers: A Novel Strategy for Enhancing Transdermal Drug Delivery

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ABSTRACT
Skin penetration enhancers have been used to improve bioavailability and increase the range of drugs to be administered by topical and transdermal routes. Enhancement in skin penetration via modification of the stratum corneum by hydration, or by use of chemical enhancers acting on the stratum corneum lipids and keratin, partitioning and solubility effects. The mechanism of action of penetration enhancers is used as an aid in potential clinical applications. Synthetic chemicals generally used for this purpose are rapidly losing their value in transdermal patches due to reports of their absorption into the systemic circulation and subsequent possible toxic effect upon long term application. Terpenes are included in the list of Generally Recognized as Safe (GRAS) substances and have low irritancy potential. In this review, we have discussed the chemical penetration as well as natural penetration enhancement technology for transdermal drug delivery as well as the probable mechanisms of action.

KEYWORDS: Penetration enhancers, Terpenes, Transdermal, Bioavailability.

INTRODUCTION
The skin has attracted much attention as an alternative route for administering systemically active drugs, but its potential use is often hindered by poor tissue permeability, predominantly attributed to the outermost layer of the skin, the stratum corneum (SC). This layer provides a protective barrier that prevents the loss of physiologically essential substances and limits the diffusion of potentially toxic chemicals from the external environment into the body. Different methods have been used to overcome the barrier property of the SC. This is usually achieved by incorporation of certain chemicals or derivatives as permeation enhancers in the formulation which act as nontoxic promoters for enhancing percutaneous absorption. The success of a dermatological drug to be used for systemic drug delivery depends on the ability of the drug to penetrate through skin in sufficient quantities to achieve the desired therapeutic effect.

Penetration Enhancers
Penetration enhancers are used to promote the drug transport across the skin barrier. There are numerous mechanisms to increase penetration enhancement. The interaction of the enhancers with the polar head groups of the lipids is the possible way to increase the penetration. The lipid-lipid head group interactions and the packing order of the lipids are changed which cause the facilitation of the diffusion of hydrophilic drugs. Penetration enhancer’s increases the content of free water molecules between the bilayer, which cause to an augmentation of the cross-section for polar drug diffusion.

Function of Penetration Enhancers
On the basis of 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 make it permeable to drugs. Many enhancers operate mainly in this way e.g., Azone, terpenes, fatty acids, dimethy sulfoxide (DMSO) and alcohols.
2. Protein modification: Ionic surfactants, decylmethylsulfoxide 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, co-enhancer and cosolvents. Ethanol enhances the penetration of nitroglycerin and estradiol through the stratum corneum.

Properties of Penetration Enhancers
Some of the more desirable properties for penetration enhancers acting within the skin have been given as:

- They should be non-toxic, non-irritating and non-allergenic.
- They should ideally work rapidly, and 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 unidirectional i.e. should allow therapeutic agents into the body whilst preventing the loss of endogenous material from the body.
- The penetration enhancers should be compatible with both excipients and drugs.
- They should be cosmetically acceptable with an appropriate skin ‘feel’.

Pathway of Transdermal Permeation
Permeation can occur by diffusion via:
1. Transdermal permeation, through the stratum corneum.
2. Intercellular permeation, through the stratum corneum.
3. Transappendaged permeation, via the hair follicle, sebaceous and sweat Glands.

Most molecules penetrate through skin via intercellular micro route and therefore many enhancing techniques aim to disrupt or bypass its elegant molecular architecture.

Events Governing Percutaneous Absorption
The process of percutaneous absorption can be described as follows (fig1). When a drug is applied topically the drug is diffuses passively out of its carrier or vehicle and, depending on where the molecules are placed down, it partitions in to either the stratum corneum or the sebum filled ducts of the pilosebaceous glands. Inward diffusive movement continues from these locations to the viable epidermal and dermal points of entry. In this way a concentration gradient is established across the skin up to the outer reaches of the skin microcirculation where the drug is swept away by the capillary flow and readily distributed throughout the body.

Types of Penetration Enhancers
There are three types of penetration enhancers (Table 1)

(1) Drug vehicle based: Drug-vehicle based method of penetration enhancement does not change stratum corneum function like chemical and physical penetration enhancement method. This method is based on drug selection, vesicles and particles, prodrug, chemical potential of drug and ecteuvic system. The interaction of enhancers with the stratum corneum and the development of structure activity relationships for enhancers will aid in the development of enhancers with optimal characteristics and minimal toxicity.

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Chemical penetration enhancers: Chemical penetration enhancers are also called as absorption promoters or accelerants. The properties of ideal chemical penetration enhancer are to be pharmacological inert, nontoxic, nonirritating, non allergic, rapid onset of action, and suitable duration of action according to drug, inexpensive and cosmetically acceptable. Chemical penetration enhancers insert themselves directly between the hydrophobic lipid tails and change lipid packing which cause lipid fluidity and increase the drug permeation.

Physical penetration enhancers: There are numerous physical and electrical methods were used for penetration enhancer. These include iontophoresis (by a small direct current –approximately 0.5 mA/cm²), phonophoresis (by low frequency ultrasound energy increases lipid fluidity), electroporation (by application of short micro- to milli-second electrical pulses of approximately 100-1000 V/cm to create transient aqueous pores in lipid bilayer) and photomechanical waves (laser-generated stress waves reported to cause a possible transient permeation of the stratum corneum) 12.

A Brief Review Of Various Penetration Enhancers

The various types of chemicals have been used as a chemical penetration enhancer, some of the most commonly used penetration enhancers are discussed below and their effects in different formulations are shown in Table 3.

Pyrrolidones

Pyrrolidones have been used as permeation enhancers for numerous molecules including hydrophilic (e.g. mannitol and 5-flouroacil) and lipophilic (propylene 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 patch13. 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 corneum over extended time periods4.

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 permeation17,18. 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-decloxazolidin-2-one has been reported to localize the delivery of many active ingredients such as retinoic acid and diclofenac sodium in skin layers19.

Urea

Cyclic urea permeation enhancers are biodegradable and non-toxic molecules consisting of a polar parent moiety and a long chain alkyl ester group. As a result, enhancement mechanism may be a consequence of both hydrophilic activity and lipid disruption mechanism20.

Azone

Azone (1-dodecylazacycloheptan-2-one or laurocapran) was the first molecule specifically designed as a skin penetration enhancer. Azone is a colorless, odorless liquid with a melting point of -7 °C and it possesses a smooth, oily but 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%20. 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 lipid or separate domains within the bilayer20.

Sulfoxide and similar compounds

Dimethyl sulfoxide (DMSO), the most important compound belonging to the category of sulfoxide and similar compounds, enhances the transdermal permeation of a variety of drugs, like β-blockers, ephedrine hydrochloride, and papaverine hydrochloride21,22. It also enhances the release of azapropazone from its ointments. Fourier transforms, Raman spectroscopic studies revealed that DMSO changes the stratum corneum keratin from alpha-helical to β-sheet conformation. At concentrations greater than 60% v/v, at which DMSO enhances the flux, there was evidence of its interaction with stratum corneum lipids23.

Fatty acid

Oleic acid is a mono-unsaturated fatty acid and is reported to increase the permeation of lipophilic drugs through the skin and buccal mucosa by transdermal cellular pathway24. Most of these molecules when applied onto the skin surface permeate along the SC lipid domain and the organization of these regions is very important for the barrier function of the skin. The SC lipid composition and organization differ from that of other biological membranes, with long chain ceramides, free fatty acids, and cholesterol and cholesteryl esters being the main lipid classes25.

Alcohol, glycol, and glycerides

Alcohols have so many uses such as a vehicles, solvents or permeation enhancers in improving transdermal delivery of drugs. These include alkanols, alkenols, glycols, polyglycols and glycerol’s26. Low molecular weight alkanols are thought to act as solvents, enhancing the solubility of drugs in the matrix of the stratum corneum. Disruption of the stratum corneum integrity through extraction of biochemistry’s by the more hydrophobic alcohols almost certainly also contributes to enhanced mass transfer through this tissue. The molecular complexity of different glycol molecules is a determinant of their efficacy as permeation enhancers. Solubility of the drug in the delivery vehicle is markedly influenced by the number of ethylene oxide functional groups on the enhancer molecule. This solubility modification may either enhance or retard transdermal flux depending on the specific drug and delivery environment. Glycerides are also effective as permeability enhancers. They are used in combination with ethanol as a cosolvents27.

Alkyl-n, n-disubstituted amino acetates

Dodecyl-N, N dimethylaminoacetate and dodecyl-2-methyl-2-(N, N-dimethylaminoacetate) (DDAIP) are introduced as skin permeation enhancer. These are insoluble in water, but soluble in organic solvents and in water and alcohol mixtures. The penetration enhancing activity is decreased by increasing the N, N-dialkyl carbon chain. The skin-irritating potential of the amino acetates is very less, due to the biochemical decomposition of these enhancers by the skin enzymes to N, N-dimethyl glycine and the corresponding alcohols. Skin penetration is increased by the interaction with stratum corneum keratin and it increases the hydration efficiency resulting from these interactions28.

Surfactants

As with some of the materials described previously surfactants are found in many existing therapeutic, cosmetic and agro-chemical preparations. Usually, surfactants are added to formulations in order to solubilise lipophilic active ingredients, and so they have potential to solubilise lipids within the stratum corneum. Typically composed of a lipophilic alkyl or aryl fatty chain, together with a hydrophilic head group, surfactants are often described in terms of the nature of the hydrophilic moiety. Anionic surfactants include sodium lauryl sulphate (SLS), cationic surfactants include cetyltrimethyl ammonium bromide, the nonoxynol surfactants are non-ionic.

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surfactants and zwitterionic surfactants include dodecyl betaine. Anionic and cationic surfactants have potential to damage human skin. SLS is a powerful irritant and increased the transepidermal water loss in human volunteers in vivo and both anionic and cationic surfactants swell the stratum corneum and interact with intercellular keratin. In spite of their fairly satisfactory performance in enhancing the permeation of drug molecule across the skin, chemical enhancers are viewed with wariness in transdermal formulations due to their irritancy potential when employed at concentrations necessary for achieving useful levels of penetration enhancement. Efforts have been directed at identifying safe and effective enhancers from both natural products and synthetic chemicals. In particular, terpenes from natural sources and laboratory designed terpenoids have attracted great interest. Terpenes are generally considered to be less toxic with low irritancy potential compared to surfactants and other synthetic skin penetration enhancers. Further, quite a few terpenes are included in the list of Generally Recognized as Safe (GRAS) agents issued by US FDA.

Essential Oil, Terpenes And Terpenoids

Terpenes and terpenoids are usually the constituents of volatile oil. Several natural sources and their major terpenes content are summarized in Table 2. The basic chemical structure consists of a number of repeated isoprene (C5H8) units, which is used to classify terpenes. Thus, monoterpenes have two isoprene units (C10), sesquiterpenes have three (C15), and diterpenes have four (C20), etc. Terpenes may also be classified as acyclic/linear, monocyclic and bicyclic. Numerous terpenes have long been used as medicines as well as flavoring and fragrance agents. The essential oils of eucalyptus, chenopodium and ylang-ylang have been found to be effective penetration enhancers for 5-flourouracil transfusing human skin in vivo. Cornwell et al investigated the effect of 12 sesquiterpenes on the permeation of 5-flourouracil in human skin. One mechanism by which this agent operates is to modify the solvent nature of the stratum corneum, thus improving drug partitioning into the tissue.

Cineole

Eucalyptol is a natural organic compound which is a colorless liquid. It is cyclic ether and a monoterpennoid. Eucalyptol is also known by a variety of synonyms: 1,8-cineol, 1,8cineole, limonene oxide, cajeputol, 1,8-epoxy-pmenthan-1, 8-oxido-p-menthan, eucalyptol, eucalyptol, 1,3,3-trimethyl-2- oxabicyclo[2,2,2]octane, cineol, cineole. Eucalyptol suppository is used for the treatment of some respiratory ailments. Because of its pleasant spicy aroma and taste, eucalyptol is used in flavorings, fragrances, and cosmetics. It is also an ingredient in many brands of mouthwash and cough suppressant. 1, 8-Cineole has been used to promote the percutaneous absorption of several lipophilic drugs through hairless mouse skin.

Eugenol

Eugenol is a member of the allylbenzene class of chemical compounds. It is a clear pale yellow oily liquid extracted from certain essential oils especially from clove oil, nutmeg, cinnamon, and bay leaf. It is slightly soluble in water and soluble in organic solvents. It has a pleasant, spicy, clove-like odour. Cloves are the aromatic dried flower buds of a tree in the family Myrtaceae. It is native to Indonesia and used as a spice in cuisines all over the world. Eugenol, a component of clove, may reduce the ability to feel and reacting to painful stimulation. Therefore, use of clove products on the skin with other numbing or pain-reducing products such as lidocaine / prilocaine cream, theoretically it may increase effects. FT-IR and partitioning studies reveal that the enhancement in the permeability coefficient of drug by Eugenol is due to lipid extraction and improvement in the partitioning of the drug to the SC.

Farnesol

Farnesol is a sesquiterpene alcohol, present in many essential oils, such as citronella, neroli, cycam, lemon grass, tuberose, balsam, and tolu. It is used in perfumery to emphasize the odors of sweet floral perfumes. It has been reported that farnesol (0.25%, v/v) enhances the permeation of diclofenac sodium, with respect to other terpenes, in the following order: farnesol > carvone > nerolidol > menthone > limonene. However, at 2.5% (v/v) concentration nerolidol was found to be the best candidate with a 198-fold increase in the permeability coefficient of diclofenac sodium followed by farnesol with a 78-fold increase in permeation.

Menthol

Menthol is obtained from flowering tops of Mentha piperita. The main form of menthol occurring in nature is (+)-menthol. It is frequently used in antipruritic creams and as an upper respiratory tract decongestant. Menthol has been a traditional and arguably, the most effective penetration enhancer that along with limonene can be considered as the prototype for the use of terpenes as penetration enhancers. It has been used as an enhancer for transdermal delivery of variety of drugs including imipramine hydrochloride, caffeine, hydrocortisone, triamcinolone, propanolol hydrochloride etc. Synergistic application of terpenes with iontophoresis has also been described in the literature; terpenes, such as menthol, cineole, and terpineol, when used along with iontophoresis have been shown to increase the flux of buspirone hydrochloride by more than 200-fold compared to a 15-fold increase using iontophoresis alone. Of the above-mentioned terpenes, menthol yielded a higher flux compared to cineole and terpineol.

Camphor

Camphor is a waxy, white or transparent solid with a strong, aromatic odour. It is a terpenoid with the chemical formula C10H16O. It is found in wood of the camphor laurel (Cinnamomum camphora). It also occurs in some other related trees in the laurel family, notably Ocotea usambarensis. It can also be synthetically produced from oil of turpentine. It is also used in medicinal purposes. Camphor is readily absorbed through the skin and produces a feeling of cooling.

D-limonene

D-Limonene is obtained as a by-product of the citrus juice industry. It is the major component of the oil extracted from the rinds of citrus fruits. There are two main grades of d-limonene which are called food grade and technical grade. When citrus fruits are juiced, the oil is extracted out of the rind. The juice is separated from the oil and the oil is distilled to recover certain flavour and fragrance compounds. This is called food grade d-limonene which is 96% to 97% pure and has a mild orange aroma.

CONCLUSION

Skin permeation enhancement technology is a rapidly developing field which would significantly increase the number of drugs suitable for transdermal drug delivery, with the result that skin will become one of major routes of drug administration in the next decade. Research in this area has proved the usefulness of Penetration enhancers in the enhancement of drug permeation through skin. Chemical penetration enhancers are not only specific towards stratum corneum; they also penetrate into the deeper layers of the skin to viable epidermal cells and induce skin irritation responses. Numerous chemical compounds have been evaluated for penetration-enhancing activity, and different modes of action have been identified for skin penetration enhancement. Potential substances have been used for drug penetration-promoting effects with a low or no skin irritating potential. Terpenes, the naturally occurring volatile oils, appear to be clinically acceptable penetration enhancers as indicated by high percutaneous enhancement ability, reversible effect on the lipids of SC, minimal percutaneous irritancy at low concentration (1–5%) and good...
evidence of freedom from toxicity. But still, a lot of work has to be done in the field of penetration enhancers.

REFERENCES
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Table1: Types of penetration enhancers

<table>
<thead>
<tr>
<th>Sr. no</th>
<th>Drug vehicle based</th>
<th>Chemical penetration Enhancer</th>
<th>Physical method</th>
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<tbody>
<tr>
<td>1</td>
<td>Drug selection</td>
<td>Sulphoxides</td>
<td>Iontophoresis</td>
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<tr>
<td>2</td>
<td>Vesicles and particles</td>
<td>Alcohols</td>
<td>Ultrasound (phonophoresis and sonophoresis)</td>
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<tr>
<td>3</td>
<td>Predrug and ion pair</td>
<td>Polyols</td>
<td>Electroporation</td>
</tr>
<tr>
<td>4</td>
<td>Chemical potential of drug</td>
<td>Alkene</td>
<td>Radio frequency</td>
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<tr>
<td>5</td>
<td>Eutectic systems</td>
<td>Fatty acids</td>
<td>Thermophoresis</td>
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<tr>
<td>6</td>
<td>Complexes</td>
<td>Esters</td>
<td>Suction aiblation</td>
</tr>
<tr>
<td>7</td>
<td>Amines and amides</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Terpenes</td>
<td>Skin puncture and perfuration</td>
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</tr>
<tr>
<td>9</td>
<td>Surface active agents</td>
<td>Skin stretching</td>
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<tr>
<td>10</td>
<td>Pyrrolidones</td>
<td>Skin abraison</td>
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Table 2: Natural sources of terpenes

<table>
<thead>
<tr>
<th>Sr. no</th>
<th>Source</th>
<th>Botanical name</th>
<th>Major Terpenes</th>
<th>Reference</th>
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<tbody>
<tr>
<td>1</td>
<td>Apti fructus</td>
<td>Apium graveolens</td>
<td>Limonene</td>
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<tr>
<td>2</td>
<td>Cardamom</td>
<td>Elettaria cardamomum</td>
<td>1,8-Cineole, α-terpineol, α-terpinyl acetate</td>
<td>33</td>
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<tr>
<td>3</td>
<td>Fennel</td>
<td>Foeniculum vulgare</td>
<td>Trans-anethol, some terpene hydrocarbons, α-pinene, α-phellandrene</td>
<td>33</td>
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<tr>
<td>4</td>
<td>Melissa</td>
<td>Melissa officinalis</td>
<td>Geraniol, nerol</td>
<td>34</td>
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<tr>
<td>5</td>
<td>Orange</td>
<td>Citrus aurantium</td>
<td>d-Limonene</td>
<td>34</td>
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<tr>
<td>6</td>
<td>Eucalyptus</td>
<td>Eucalyptus globulus</td>
<td>1,8-Cineole, eucalyptol, moderate amounts of monoterpenes (α-cymene, α-pinene)</td>
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<td>7</td>
<td>Caraway</td>
<td>Carum carvi</td>
<td>(S)(+)-Carvone, (R)(−)-limonene, α-pinene, dihydrocarvone, dihydrocarveol</td>
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<td>8</td>
<td>Coriander</td>
<td>Coriandrum sativum</td>
<td>D(+)-linalool, monoterpene hydrocarbons (α-pinene, d-limonene, γ-terpinene, ρ-cymene)</td>
<td>33</td>
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Table 3: Effect of Permeation Enhancers on different Formulations

<table>
<thead>
<tr>
<th>Sr. no</th>
<th>Penetration Enhancer</th>
<th>Formulation</th>
<th>Result</th>
<th>Reference</th>
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<tbody>
<tr>
<td>1</td>
<td>Sulphoxides</td>
<td>Transdermal patches of Ropinirole HCl.</td>
<td>Highest permeation coefficient was achieving using DMSO in formulation.</td>
<td>44</td>
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<td>2</td>
<td>Pyrrolidones</td>
<td>Transdermal delivery of bupranolol in rabbits</td>
<td>Increased the in vivo delivery of buspropanol, thereby increased the beta-blocking activity</td>
<td>45</td>
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<tr>
<td>3</td>
<td>Menthol as enhancer</td>
<td>Ibuprofen gel</td>
<td>In vivo enhancement due to vasodilator effect of menthol</td>
<td>46</td>
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<tr>
<td>4</td>
<td>Azone</td>
<td>Effect of Azone on Shuangwu traumatic formula</td>
<td>Penetration enhancement was achieved by 3 (w/w) Azone</td>
<td>47</td>
</tr>
<tr>
<td>5</td>
<td>D-limonene</td>
<td>Effect of enhancers on ketorolac gel through rat skin</td>
<td>Enhanced permeation</td>
<td>48</td>
</tr>
<tr>
<td>6</td>
<td>Essential oil</td>
<td>Evaluated by penetration enhancers towards 5-fluorouracil using excised human skin</td>
<td>Eucalyptus and chenopodium both are very effective, causing a near 30-fold increase in drug permeability.</td>
<td>35</td>
</tr>
</tbody>
</table>

Fig. 1 Events governing percutaneous absorption