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Drug Penetration Enhancement Techniques in Transdermal Drug Delivery System: A Review

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Transdermal Drug Delivery System (TDDS) is described as a self-contained or discrete dosage form that is applied to the intact skin. This rout of drug administration of drugs through the skin for therapeutic use is an alternative approach to oral, intravascular, subcutaneous, and transmucosal routes. The delivery of drugs through the skin to the systemic circulation provides a convenient route of administration for a variety of clinical indications. Transdermal Drug Delivery System allows continuous drug administration, use of drugs with short biological half lives, avoids increases hepatic first pass elimination and rapid termination of medication by removing the transdermal drug delivery system from the skin. Various transdermal technologies may be applied for different categories of pharmaceuticals used for the treatment of disorders of the skin or for systemic effects to treat diseases of other organs. Several transdermal products and applications include hormone replacement therapy, contraception, pain management, angina pectoris, smoking cessation, and neurological disorders such as Parkinson's disease. The most commonly used transdermal system is the skin patch using various types of technologies. Stratum corneum is the outermost layer of the

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skin and it is the main barrier layer for permeation of drug in transdermal delivery of drugs. So, to circumvent the barrier properties of stratum corneum and to increase the flux of drug through skin membrane various penetration enhancement techniques are used in transdermal drug delivery system. The review presents different physical and chemical methods in penetration enhancement approaches and to optimize the transdermal delivery system.

Keywords: Penetration enhancement; transdermal drug delivery; pain management; angina pectoris.

1. INTRODUCTION

When a drug is applied to the skin, two consecutive physical events may become rate limiting steps in cutaneous permeation; first, release of the active compound from the vehicle and secondly, the penetration of this compound through the skin barrier. These two processes are closely related, and both are dependent on the physical properties of the drug, vehicle and barrier. [1] The stratum corneum is the main barrier to drug permeation across the skin. [2] The structure of the stratum corneum consists of several layers of keratinized corneocytes embedded in an extracellular matrix of lipids arranged in an ordered lamellar structure. The corneocytes are relatively impermeable, with the result that molecules diffusing through the stratum corneum primarily traverse a tortuous pathway through the extracellular lipid matrix. The lipophilic molecule diffuses by this intercellular route of transport, predominates over the transcellular one. For polar or ionic compounds the route of transport is less understood and it is possible that a parallel pathway to the lipophilic route exists in the skin. Hence the barrier properties of the stratum corneum originate partly from the geometry of its internal structure and partly from the diffusional resistance of its extracellular lipid structure. [3]

The enhancement of drug delivery through the skin can be possible by (1) the improvement in the drug release of drug from transdermal preparations, (2) enhancement in the flux of drug through skin or retention of the drug in skin, (3) increase in topical or localized skin delivery or tissue targeting of drugs and (4) combination of all three steps [4] The approach to enhance drug permeation across the skin focus either on altering the drug-vehicle interaction to improve partitioning into the stratum corneum or reversible modification in the structure of stratum corneum to minimize resistance to drug diffusion [5]. These approaches are shown in Table 1 and discussed as bellow

2. VEHICLE DRUG INTERACTION

2.1 Thermodynamic Activity

The steady-state flux of a drug through skin is as

$$(\mathrm{dM/dt}) = (\mathrm{DPCv})/\mathrm{h} \quad (1)$$

Where , (dM/dt) is the cumulative amount of permeant passing per unit area of membrane (flux), D is the diffusion coefficient, C_v is the concentration of the drug in the vehicle, P is the partition co-efficient between the membrane and the vehicle and h is membrane thickness. Higuchi rewrote this equation in terms of thermodynamic activities as..

$$(\mathrm{dM/dt}) = \mathrm{aD}/\Upsilon\mathrm{h} \quad (2)$$

Table 1. Approach to Enhance Drug Permeation Across Skin

S. No.	Approach to Enhance Drug Permeation Across Skin	
1	Vehicle Drug Interaction	1. Thermodynamic Activity, 2. Prodrug, 3. Ion Pairing, 4. Eutectic System
2	Stratum Corneum Modification.	1. Skin Hydration, 2. Use of permeation enhancer
3	Stratum Corneum Bypass	1. Tape stripping, 2. Stratum corneum ablation, 3. Microniddle 4. Microdermabrasion
4	Energy Driven Methods	1. Ultrasound, 2. Iontophoresis, 3. Electroporation, 4. Jet injection
5	Vesicles and Particles.	1. Liposomes and analogues, 2. Nanoparticles

Where, a is the thermodynamic activity of the permeant and Υ is effective activity coefficient in the membrane. The maximum flux of a drug across a membrane occurs when the drug is at its highest thermodynamic activity. At saturation, equilibrium exists between the solid and liquid phase and activity equals 1.

A suspension containing finely grounded drug in vehicles behaves as saturated solutions of drug. An activity can exceed unity when supersaturated systems are formed. The degree of saturation of solution is calculated by dividing the drug concentration in prepared solution by saturated solubility in the same solvent mixture. Generally, the co-solvent method is used in preparing a supersaturated system. Saturated solutions of co-solvent mixture are mixed with a poor solvent during preparation of supersaturated system. To avoid drug crystallization in supersaturated solution and hence to maintain supersaturated state, polymers like polyvinyl pyrrolidone have been used as antinucleants. Crystallization of a steroid drug formulated in a matrix-type patch containing PVP, was delayed for a further 6 months compared to a patch void of an antinucleant [5,6].

2.2 Prodrug

Prodrugs are compounds which are inactive in their parent form. After administration, the parent drug is chemically transformed to active metabolites, which exert the pharmacological effect. This strategy involving bioreversible chemical modification to modify the physicochemical property of a drug is also being increasingly used to optimize dermal and transdermal delivery because regeneration of parent compound occurs by the enzymatic processes. A promising prodrug strategy is to derivatize the drug with a promoiety that possesses inherent ability to enhance the permeation [7]. Prodrugs are generally designed to enhance the lipophilicity of the parent drug, thus increasing skin partitioning. The most common prodrug strategy is to covalently link an active drug with an inactive moiety via an ester bond. Following administration, non-specific skin esterases cleave the active drug. The prodrug approach has been used to increase delivery of a range of drugs across the skin including propranolol [7] naltrexone [8,9], α-Tocopherol pro-vitamin [10].

2.3 Ion Pairing

The ionized drugs do not readily permeate across human skin and their permeation coefficient has been estimated to be approximately 10^4 times smaller than for the respective unionized species [11]. In an ion-pair technique, oppositely charged species were added to a charged drug which forms an ion-pair in and the charges are neutralized. The ion-pair should partition and diffuse through the stratum corneum, before dissociating in the viable epidermis, thereby releasing the active drug. The enhancement in penetration of salicylic acid observed using the ion-pair strategy. In an equimolar mixture of salicylic acid and various alkyl amines solution, conductivity was reduced, indicating ion-pair formation. The ion-pairing strategy has also been employed to enhance skin penetration of 5-aminolevulic acid, retinoic acid and ondanestron [5].

2.4 Eutectic System

The steady-state flux of drug across a membrane is directly proportional to the solubility of a drug in lipid phase of the membrane. In case of ideal solution, the log solubility of drug in a given solvent is directly related to the reciprocal of melting point of drug [12,13]. (Equation 3)

$$\mathrm{LogCp} = (\mathrm{Constant} + \Delta\mathrm{Hd})/2.0303\mathrm{RTm} \quad (3)$$

Where, C_p is the mole fraction solubility of the drug, ΔHd is the drug lattice dissociation energy, R the gas constant; and T_m the drug melting temperature. Soluble drug is the only physical form that can diffuse and a linear correlation is observed when log steady-state flux is plotted against melting point of the drug. It indicated that the penetration will be better, as the melting point is lower greater solubility [14-16].

3. STRATUM CORNEUM MODIFICATION

3.1Skin Hydration

The use water is one of the long-standing approaches to improve transdermal and topical delivery of medicaments. The water content of human stratum corneum is around 15-20 % w/w of the tissue and changes depending on the external environment such as humidity. The 15 to 20 % of water present in stratum corneum is associated with structural elements within the

tissue. This can be assessed as 'bound', water and remaining water within tissue is as 'free'. The free water is available to act as a solvent within membrane for polar permeants. The human skin contains a hygroscopic humectant mixture of various amino acids, amino acid derivatives and salts. These are termed as the natural moisturizing factor NMF, which retains water within the stratum corneum and helps to maintain tissue pliability. The keratin-filled corneocytes containing functional groups such as -OH and -COOH can also bind water molecules within the tissue. Upon hydration either by soaking the skin in water, exposing membrane to high humidities or occluding the tissue, the water content of stratum corneum to reaches in equilibrium with underlying epidermal skin cells. It can approach 400 % of the tissue dry weight. [17].The elevated water content of the stratum corneum leads to formation of water pools in the intercellular lipid matrix (ILM). This tends to lose lipid packing and increasing mobility of the chains. The hydration of stratum corneum can be improved by occlusion of several chemicals, e.g. components of the "natural moisturizing factor" such as pyrrolidones and urea, application of a low or high voltage potential. The penetration of both hydrophilic and hydrophobic drugs can be increased by hydration of stratum corneum [18,19].

3.2 Use of Permeation Enhancer

As the skin can be an attractive rout of administration of drugs due to ease of access and its prevalence, since last few decades the goal of researchers has been focused in development of efficient delivery of drugs into, and across the skin. [20] In transdermal delivery, when skin permeation of drugs is high, the penetration rate of drugs though skin can be controlled by modifying the drug release from the systems and in case of poorly permeable drugs, effective enhancers should be included in the system to enhance the skin absorption of these drugs. [21] The use of penetration enhancers is one of the approaches to overcome the problems arising from skin impermeability which reversibly remove the barrier resistance. Penetration enhancers are chemical compounds, pharmacologically inactive, but can partition into and interact with the stratum corneum intercellular lipids reducing the resistance of skin to drug diffusion. [17,22-25].

The desirable properties for penetration enhancers acting within skin are as

1. It should be non-toxic, non-irritating, and non-allergenic.
2. The activity and duration of effect should be predictable and reproducible.
3. The penetration enhancers should work unidirectionally i.e. should allow therapeutic agents into the body.
4. The barrier properties of the skin should return both rapidly and fully after the removal of transdermal or topical drug delivery system from the skin.
5. The penetration enhancers should be cosmetically acceptable and compatible with both excipients and drugs.
6. A large number of other chemicals have been evaluated as potential permeation enhancers discussed as bellow.

3.3 Alcohol Enhancers

Ethanol, a short chain alcohol (C_2-C_5) is one of the most commonly used permeation enhancers in formulation of transdermal drug delivery system. A number of mechanisms have been proposed for permeation enhancing activity of ethanol. As a solvent, ethanol can be included in the formulation to enhance the solubility of the poorly soluble drug. In addition, ethanol is thought to alter the solubility properties by extracting the lipids in the stratum corneum thus facilitating improved drug partitioning. The first commercial transdermal system Estraderm®, containing estradiol was to use ethanol as a permeation enhancer. As short-chain alcohols are very readily absorbed by the skin and large amounts of alcohol are required to obtain a prolonged enhancement effect which may produces skin irritation. The short-chain alcohols are used in combination with other components or as dilute solutions to minimize irritation. The long-chain alcohols (C_{10}-C_{25}) may act by plasticizing the skin. The amount of long chain alcohol required to produce enhancement is much less than when ethanol is used. *n*-dodecanol is most frequently long chain alcohol used for penetration enhancement effect.Third group of alcohol-based enhancers are multifunctional or polyalcohols alcohols. Propylene glycol and glycerol are two polyalcohols enhancers which are frequently used to lower the irritation effect of other enhancers. Glycerol and polyglycerol ethers are used alone and in combination with propylene

glycol to increase skin absorption, and to decrease the irritating effect of C_2 and C_3 alcohols, Azone®, and other compounds [26,27].

3.4 Amide Enhancers

In this category, dimethylacetamide was the first compound to be used as penetration enhancers. This amide, in combination with other aprotic solvents, has been shown to enhance skin permeation by interacting with skin lipids. Although dimethylacetamide is having a great enhancing property, it is generally thought to be too irritating as an enhancer. The amides with longer aliphatic chains are preferred, either alone or in combination with other enhancers. Other examples of this group are NJ-di-n-propy dodecanamide and N-butyl-N-dodecyl acetamide [26].

3.5 Amino Acid Enhancers

Amino acids and water soluble proteins can enhance the percutaneous absorption of drugs. The N-alkyl-amino acids improve drug absorption by loosening the skin's keratin layer. For example L (α)-amino acids in 40% ethanol enhances the penetration of steroidal contraceptives levonorgestrel and estradiol [26].

3.6 Azone and Azone-Like Enhancers

The first molecule designed as a skin penetration enhancer is azone. Chemically it may be a hybrid of a cyclic amide, as with pyrrolidone structures with an alkyl sulphoxide. It is a colorless, odorless liquid with a melting point of 7 ^{0}C and possesses a smooth, oily but yet no greasy feel. Azone is a highly lipophilic material with a log $P_{octanol/water}$ about 6.2. It is miscible with most organic solvents including alcohols. It has low irritancy, very low toxicity oral LD in rat of 9 g/kg and little pharmacological activity an antiviral effect. Azone (1-dodecylazacycloheptan-2-one or laurocapram) may exert its penetration enhancing effects through interactions with the lipids of the stratum corneum**.** It consist a large polar head group and lipid alkyl chain. It may partitions into the bilayer lipids of stratum corneum to disrupt their packing arrangement. It is used as penetration enhancer for drugs including steroids, antibiotics and antiviral agents. The penetration enhancing efficacy of Azone is strongly concentration dependent and is also influenced by the type of vehicle used. As penetration enhancer, azone is most effective at low concentrations, being employed typically between 0.1% and 5%, mostly between 1% and 3% [17,28].

3.7 Essential Oil Enhancers

Terpenes are a series of naturally occurring compounds consists of isoprene (C_5H_8) units [29]. These are grouped according to the number of isoprene units. Terpenes are further sub-divided into chemical classes of hydrocarbons, alcohols, oxides and ketones [30]. They are found in essential oils, and do compounds comprise only carbon, hydrogen and oxygen atoms, yet which are not aromatic. Numerous terpenes have long been used as medicines, flavorings fragrance agents. For examples, menthol is traditionally used in inhalation pharmaceuticals, as mild antipruritic in emollient preparations and L-menthol used to facilitate in vitro permeation of morphine hydrochloride through hairless rat skin, menthone or limonene in combination used to improve the permeation of propranolol hydrochloride [23]. As percutaneous enhancers, they may act by disrupting the ordered lipid structure of the stratum corneum and by increasing partitioning of the drug from its aqueous vehicle into the stratum corneum. The range of log P values for terpenes is wide from1 up to 6 and there is a linear relationship between log P and enhancement effect towards penetration of model drugs. Alone or in mixtures with co-enhancers, terpenes promote percutaneous penetration of lipophilic as well as hydrophilic drugs. Use of naturally occurring terpenes is reported in combination with more traditional enhancers, such as DMSO and Azone, to avoid the side-effects associated [17,26,31-33].

The combination of iontophoresis with a chemical enhancer may permit the use of lowest quantities of drug, enhancer, current or applied voltage drop within the delivery system, and hence potentially circumventing adverse reactions, toxicity problems, and irreversible structural changes. The pretreatment effects of terpenes like carvone, pulegone, cineole and menthol in ethanol and iontophoresis on the in vitro permeation of arginine vasopressin increased the flux through rat skin [34].

Similarly, volatile oils in combination with iontophoresis showed the increase in the

permeation of drugs. For example, after the pretreatment of rat skin and human skin with cardamom oil, in vitro iontophoretic permeation study showed increases in permeability of diclofenac released from PVP-HPMC binary system. There was a 10-fold increase in diclofenac flux compared to the non-treated group. Cardamom oil can be combined with iontophoresis showed a determined effect of diclofenac with less electrical current and also reduces the possibility of skin damage [35].

3.8 Fatty Acid and Fatty Acid Ester Enhancers

The fatty acids are carboxylic acids, often with long unbranched aliphatic chains. Long chain fatty acids can be used to increase the percutaneous absorption of drug. Examples of fatty acids employed as penetration enhancers include lauric acid, linoleic acid and oleic acid. Oleic acid is most commonly used in penetration enhancement technique of drug. The penetration enhancement can be influenced by the number, position and type (cis/trans) of double bonds. Saturated fatty acids for example capric acid C_{10} , lauric acid C_{12} and myristic acid C_{14} are used as penetration enhancers for some drugs, such as captopril, naloxone, thiamine disulfide and sodium nonivamide acetate [36,37]. The unsaturated fatty acids having the 'cis' configuration are more effective as drug penetration enhancers. The '*cis'* double bonds introduces a 'kink' into the alkyl tail and the bent or 'kinked' tail to may cause disruption to lipid bilayers than the straight 'trans' configuration fatty acids, which differ little from saturated fatty acids. The alkyl chain length is also of significance, with C_{10} and C_{12} carbon chain lengths providing greatest permeation enhancement. The *cis*-unsaturated fatty acids lower the main phase transition temperature (T_m) as they preferentially partition into the fluid phase [17,22,38].

3.9 Macrocyclic Enhancers

Macrocyclic compounds enhance skin absorption by temporarily increasing the solubility of the drug in the skin. The skin returns to its normal state as the enhancer is removed. Examples of this class are cyclopentadecanone and cyclopentadecanolide. The use of cyclodextrins is also reported as enhancers in transdermal drug delivery system. Hydroxypropyl β-cyclodextrinCD HP- β-CD and partially methylated β-cyclodextrin PM β-CD were used as penetration enhancers for potent beta-blocking agent like bupranolol [26,39]. Cyclodextrins when included in transdermal drug delivery, the enhancement of drug release and/or permeation may be due to change in drug thermodynamic activity in vehicles as well as its skin-vehicle partition coefficients [40].

3.10 Phospholipid and Phosphate Enhancers

The phospholipids in the form of vesicles like liposomes are used to carry drugs into and through human skin. The mechanism of phospholipids is unknown, but these may act by interacting with stratum corneum packing. This may be expected when considering their physicochemical properties and structures. However, when applied topically, phospholipids can occlude the skin surface and can increase tissue hydration, which can increase drug permeation. The penetration nhancement properties of dialkyl phosphates, particularly ditetradecyl phosphate, are reported in literature. The flux of indomethacin through rat skin and theophylline through hairless mouse skin was enhanced by phosphatidyl-choline. Similarly, hydrogenated soy bean phospholipids have been reported to enhance diclofenac permeation through rat skin *in vivo* [17,26].

3.11 2-Pyrrolidone Derivatives

Pyrrolidones apparently have greater effects on drugs having hydrophilic properties than for lipophilic. N-methyl-2 -pyrrolidone NMP and - pyrrolidone P are the most widely studied enhancers of this class. N-methyl- 2 -pyrrolidone is a polar aprotic solvent. It is used to extract aromatic moieties from oils, olefins and animal feeds. It is a clear liquid at room temperature and is miscible with most solvents including water and alcohols. -pyrrolidone is a liquid above C and miscible with most solvents including water and alcohols. -pyrrolidone is also used in commercial use as a solvent in oil production, sugars, iodine and polymers. Pyrrolidones showed the increased permeation effect in case of hydrophilic molecules like mannitol, 5 - fluorouracil and sulphaguanidine and lipophilic betamethasone- 17-benzoate, hydrocortisone, progesterone. The pyrrolidones may act by altering the solvent nature of the membrane and

used to generate 'reservoirs' within skin membranes [17,27].

3.12 Soft Penetration Enhancers

The enhancer compounds in this category are designed to degrade into nontoxic compounds after absorption. Typical examples of these are the cyclic derivatives of dioxane and dioxolane. The enhancement properties have been tested on rat skin and penetration enhancements of 2 to 8 fold were observed with drugs such as indomethacin. The structures are shown below [26].

3.13 Sulphoxide Enhancers

Dimethyl sulphoxide is a powerful aprotic solvent. It is colorless, odorless and hygroscopic in nature. It is often used in many areas of pharmaceutical sciences as a 'universal solvent'. Dimethyl sulphoxide is one of the most widely studied penetration enhancers. It is applied topically to treat systemic inflammation and currently used only to treat animals. For example, DMSO is used as penetration enhancer for piroxicam and ibuprofen [41] and Lincomycin hydrochloride, an antibiotic. [42] As penetration enhancers the mechanisms of action of DMSO is complex. It may denature proteins and on application to human skin has been shown to change the intercellular keratin confirmation, from α-helical to a β- sheet. It may also interact with the head groups of some bilayer intercellular lipid domains of human stratum corneum to distortion in the geometrical packing. DMSO interacts with the lipids. Even though it used widely as penetration enhancer, it has some disadvantages. The penetration enhancement effects of DMSO are concentration dependent and the co-solvents containing more than 60% DMSO are required for optimum enhancement efficacy. At this concentrations DMSO can cause erythema and may denature some proteins. Analogues of DMSO like dimethylacetamide (DMAC) and dimethylformamide (DMF) were developed and these solvents possesses similar powerful aprotic solvents properties, structures akin to that of DMSO and broad range of penetration enhancing activity [17,26].

3.14 Miscellaneous Enhancers

The substances described as penetrant or permeation enhancers in various patents cannot be conveniently categorized with other enhancer groups [17,26]. Hence they are mentioned as

3.15 Oxazoline and Imidazoline Derivatives

These derivatives may be used to enhance transdermal penetration of a wide variety of drugs, and also to enhance penetration into seeds of substances that enhance plant growth, such as micronutrients and chemical hybridization agents. For example.2-dodecyl-oxazoline.

3.16 Imidazole Derivatives

This group of enhancers is preferred for use with antihistamines, sympathomimetic amines, metaproterenol, diuretics such as hydrochlorothiazide, and antitussives such as dextramethorpham HBN, anti-inflammatories, and analgesics. For example 1, 2-dimethyl imidazole.

3.16.1 Oxazolidinones

For example as 4-decyl oxazolidin-2-one

3.16.2 m-Proline esters

These esters are used in combination with polar compounds such as ethanol, glycols, and methyl pyrrolidone for delivery of propranolol. For example proline n-dodecyl ester.

3.16.3 Imidazolinone and 4-imidazolin-2-one derivative

These compounds are useful as skin penetration enhancers, especially for beta lactam antibiotics, aminoglycosides, antineoplastics and antiviral agents. For example 1 -decyl-3-methyl-2-imidazolinone.

3.16.4 N-Alkanoyl cyclic amines

For example,1-dodecanoyl-2- carboxy-pyrrolidin.

3.16.5 Urethane compounds

These compounde are formed from reactions with diisocyanates and glycols or polyethers and hydroxy-known as urethane.

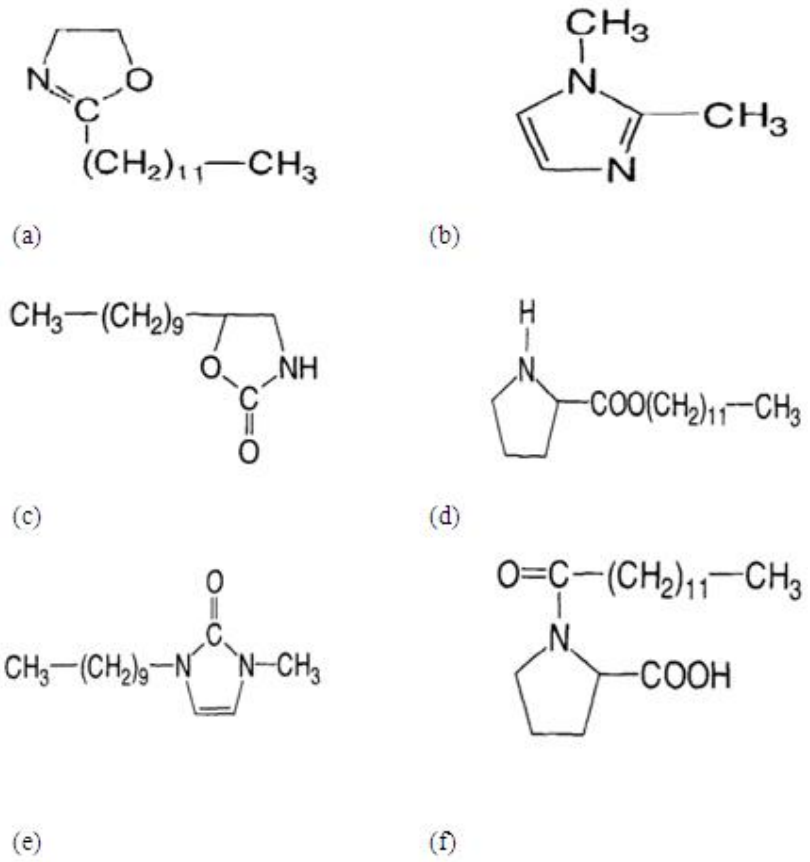

Fig. 1. Miscellaneous enhancers. (a) 2-dodecyl-oxazoline,(b): 1, 2-dimethyl imidazole, (c): 4-decyl oxazolidin-2-one,(d): proline n-dodecyl ester, (e): 4-imidazolin-2-one and (f): 1-dodecanoyl-2-carboxy-pyrrolidin

3.17 Surfactants

The absorption of steroids, anti-inflammatories, and antihistamines is enhanced by the use of anionic, nonionic, and amphoteric surfactants. Both anionic and cationic surfactants cause swelling of stratum corneum and interact with intercellular keratin. Non-ionic surfactants are widely regarded as safe. The anionic and cationic surfactants can cause to damage human skin [40]. Sodium lauryl sulphate is a anionic surfactants. It is powerful irritant and increased the trans epidemeral water loss in human. The example of cationic surfactants is cetyl trimethyl ammonium bromide. Non-ionic surfactants generally have low chronic toxicity and most have been shown to enhance the flux of materials permeating through biological membranes, for example Tween 80.

4. STRATUM CORNEUM BYPASS

4.1 Tape Stripping

In this technique successive layers of the stratum corneum are removed by removes repeated application of adhesive tape to the skin surface. The tape stripping technique to remove the stratum corneum from human skin is widely used as a method for studying the kinetics and penetration depth of drugs. [43] The enhancement of topical penetration of both 5 - aminolevulinic acid and hexyl amino-levulinate across mouse skin in vivo was achieved successfully by tape stripping method. Although tape stripping in as inexpensive way of reducing the barrier function of the stratum corneum, it is inconvenient, shows poor reproducibility and is unlikely to be acceptable for routine use by patients [5]

4.2 Stratum Corneum Ablation

4.2.1 Thermal ablation

The transdermal permeation of drug can be achieved by thermal ablation created by the thermal ablation method using radiofrequency. Needle-like electrodes were inserted into the skin, while an alternating current at radiofrequency (100 kHz) was applied to each of the electrodes. The ions within the skin attempt to follow the change in direction of the alternating current, resulting in frictional heating and subsequent cell ablation. The microchannels formed can assist in transportation of drug. The size of microchannels would be approximately 70 μm in depth and 30 μm in diameter [22]. A long-term safety data is required to determine if repeated use of such devices can cause irreversible skin damage.

4.2.2 Suction ablation

A small blister is made on the skin using vacuum in suction ablation. The upper surface of the blister is removed using an epidermatome, which provides a pathway of low resistance for drug penetration. This technique is a multi-step process, inconvenient for routine use by patients or clinicians and time required for blister formation can be up to 2.5 h [44].

4.2.3 Laser Ablation

This technique involves direct and controlled exposure of a laser to the skin which leads to the ablation of the stratum corneum without significantly damaging the underlying epidermis and creates pores in the stratum corneum. The change in structure of the stratum corneum using this method has been shown to increase the delivery of lipophilic and hydrophilic drugs [41]. The study reports using lasor ablation method were found to reduce the onset of action of lidocaine to 3-5 minutes, while 60 minutes was required to achieve a similar effect in the control group.

4.3 Microniddle

The stratum corneum is an outermost layer of the skin functions as main barrier in delivering drugs via the skin. A means to overcome the skin barrier, avoiding the transportation through stratum corneum, is based on the formation of mechanically produced conduits through the stratum corneum by the use of an array of small needles known as microneedles arrays. The Microneedles can be either solid or hollow and can posses a plethora of geometries. These can made of varying length, as short as 25 μm and as long as 2000 μm . The base diameter of the needle and needle density can be altered. After application the microniddle penetrate across the stratum corneum and into viable epidermis. First report of microneedle assisted topical drug delivery was in the late 1950's, whereby puncturing the skin using micron-sized needles was shown to increase permeability of human skin to a model drug, calcein. There has been intense interest in this technology with significant developments being made in the field of microniddle fabrication. The flux of small compounds (MW <1000 Da) like calcein, diclofenac, methyl nicotinate and bischloroethyl nitrosourea was increased by microneedle arrays. Successful application of microneedles to increase the transport of intermediate compounds (MW between 1 and 10 kDa) like FITCV Dextran , desmopressin and insulin were reported. In addition, microneedles also had a beneficial effect of the flux of large compounds (MW >10 kDa) like bovine serum albumin, ovalbumin, antisense oligonucleotides, plasmid DNA and nanospheres [45-47].

4.4 Microdermabrasion

Microdermabrasion is one of technique to remove the stratum corneum barrier by skin abrasion and can be achieved simply by using sandpaper. This method is a widely used to alter the skin properties for cosmetic purpose.In this technique, abrasive mechanism is related to sand blasting on the microscopic scale. The increase skin permeability was observed in case of drugs like lidocaine and 5 -fluorouracil [47].

5. ENERGY DRIVEN METHODS

5.1 Ultrasound

Ultrasound is defined as sound having a frequency above 18 kHz. [48] In 1954 the combination of hydrocortisone and ultrasound technique was used successfully in treatment of digital polyarthritis. After fifty years, this technique has emerged as a powerful method to facilitate transdermal drug delivery [49].

The use of ultrasound to enhance topical or transdermal drug delivery is termed

sonophoresis or phonophoresis and has been studied for over 50 years. Ultrasound is typically divided into three frequency ranges [20-50].

1. low-frequency (18-100 kHz),
2 .therapeutic (0.7-3 MHz),
3. high-frequency (3-10 MHz)

The biological tissues medium when exposed to ultrasound, it affects via three main effects: thermal, cavitational and acoustic streaming.

1. Thermal effects: The temperature of the medium increases after absorption of ultrasound. The increase in temperature at a given frequency changes directly with the change in intensity of ultrasound and exposure time.
2. Cavitational effects: Cavitation is the formation of gaseous cavities (bubbles) in a medium upon exposure to ultrasound. The cause of cavitation is ultrasound induced pressure variation within medium. As a result of cavitation either the rapid growth and collapse of a bubble (inertial cavitation), or the slow oscillatory motion of a bubble in an ultrasound field (stable cavitation) occurs and collapse of cavitation bubbles releases a shock wave that can cause structural alteration in the surrounding tissue [36].The cavitational effects vary inversely with ultrasound frequency and directly with ultrasound intensity. Cavitation might be observed in gassy fluids or small gas-filled spaces when exposed to low-frequency ultrasound.
3. Acoustic streaming effects: The development of unidirectional flow currents in fluid in the presence of sound waves is known as acoustic streaming. This may due to ultrasound reflections and distortions occur during wave propagation. Similarly, the oscillations of cavitation bubbles may contribute to acoustic streaming. The shear stresses developed by streaming velocities may affect neighboring tissue structures [37].

Low-frequency sonophoresis has been shown to increase skin permeability to a variety of low (heparin) as well as high-molecular (insulin) weight drugs. During low-frequency Sonophoresis (frequency 20-100 kHz and pressure amplitudes 1-2.4 bar), predominantly cavitation is induced in the coupling medium (the liquid present between the ultrasound transducer and the skin) and the maximum bubble radius is estimated to be between 10 and 100 μm. The maximum radius of the cavitation bubble is proportional to the frequency and acoustic pressure amplitudes. Owing to the large bubble size; cavitation is unlikely to occur within the 15 μm thick stratum corneum during low-frequency sonophoresis. Two types of cavitations, i.e. stable or inertial cavitation plays important role in sonophoresis. Stable cavitation is periodic growth and oscillations of bubbles while inertial cavitation is violent growth and collapse of cavitation bubbles [51,52].

5.2 Iontophoresis

Enhancing molecular transport across human skin to therapeutic levels is a basic requirement in transdermal drug delivery system. [53] Due to the barrier properties of human skin, particularly the stratum corneum, most drugs do not have enough passive transdermal fluxes to achieve therapeutic effects. Therefore, physical and chemical enhancement techniques are widely used to improve skin permeability. [54] Iontophoresis is a physical enhancement technique, uses a small electric current (AC/DC) and offers good potential for the delivery of charged large molecules and chemical enhancement strategies using penetration for small molecules [55]. Most iontophoretic devices employ the constant direct current (DC) to facilitate the transport of charged or polar neutral permeants across skin. The electric field reduces skin electrical resistance by the mechanism of electroporation. In addition to electroporation, electrophoresis as a flux enhancing mechanism. The flux enhancement of neutral permeants is on the basis of electroporation without any contribution from electroosmosis, while in case of charged permeants, the flux enhancement is significantly higher due to only electroporation process. In case of AC, as current voltage is increased electroporation effect increase. [56,57] For example the iontophoretic flux was proportionally increased with concentration of drug, current density applied for ex. Rotigotine [58] Transdermal iontophoresis is useful for systemic peptide delivery due to potential advantages including the possibility to increase and regulate delivery rate of these commonly charged compounds across the stratum corneum barrier by the electric current Example. Leuprolide acetate is a nonapeptide luteinizing

hormone releasing hormone. [59] Human insulin [60].

5.3 Electroporation

Electroporation includes the use of short, high-voltage pulses has been shown to disrupt lipid bilayer structures in the skin and stratum corneum resistance rapidly and dramatically drops. The electric field correspondingly distributes to a greater extent into the deeper tissues. The electric field applied for milliseconds during electroporation, which provides an electrophoretic driving force and creates aqueous pathways, and thereby diffusion of drug through long-lived electropores for up to several hours. The percutaneous transport of the drug can be increased by orders of magnitude for small model drugs, peptides, vaccines and DNA. As the magnitude electrical resistance caused by the stratum corneum is greater than deeper tissues, the electric field applied during electroporation is initially concentrated in the stratum corneum. Electroporation technique has been studied extensively in animals, but it has received limited attention in transdermal delivery in humans because of complexity of device design [47,61,62].

5.4 Jet Injection

The use of jet injectors for delivery of drug was first explored in the early of 1930s by Arnold Sutermesiter. A jet injector is a needle free device capable of delivering electronically controlled doses of medication which finally results in improved consistency of drug delivery and reduced pain. These devices, either powder or liquid jet injections uses power source (compressed gas or a spring) to deliver drugs. Generally, employs a high-velocity jet, ranging the velocities from 100 to 200 m/s to puncture the skin to deliver the drug [63].

6. VESICLES AND PARTICLES

6.1 Liposomes and Analogues

Colloidal vesicular carriers for example, liposomes or niosomes have been extensively applied in transdermal drug delivery systems. The lipid vesicles have been widely used in various types of drug delivery systems as their potential to carry a variety of drugs. These lipid carriers can encapsulate hydrophilic drugs by loading in inner space and hydrophobic drugs in lipid area.

6.2.1 Liposomes

Liposomes are also non-toxic, biodegradable and can be readily prepared on a large scale. They are thermodynamically stable vesicles composed of one or more concentric lipid bilayers. The vesicles composed of one or more lipid bilayers arranged in concentric fashion enclosing an equal number of aqueous compartments based on the number of lipid layer they are categorized as multilamellar liposomes MLV and small unilamellar liposomes SUV. Hydrophilic drugs can be incorporated into the inner aqueous volume, whilst hydrophobic molecules can be entrapped in the lipid bilayers. Conventional liposomes are composed of phospholipid, with or without cholesterol. The most common phospholipid is phoshatidylcholine from soybean or egg yolk, with cholesterol often used to stabilize the system [5]. Liposomes offer potential value in dermal and transdermal drug delivery and recent advances and modifications generated increased therapeutic potential. Alteration in their composition and structure in vesicles resulted tailored properties. Flexible and ultradeformable liposomes claims of enhanced transdermal drug delivery to efficiencies comparable with subcutaneous administration. The advantages of topical liposome based drug formulations includes reduced serious side effects and incompatibilities due to undesirably high systemic absorption of drug, enhanced significant accumulation of drug at the site of administration ,and incorporation of wide variety of hydrophilic and hydrophobic drugs is possible.

6.2.2 Niosomes

Are lamellar structures composed of non-ionic surfactants and cholesterol. They have amphiphillic bilayer structure, such that the polar region is oriented outside and inside the vesicles where the hydrophilic drug will be entrapped and nonpolar region is formed within the bilayer. The hydrophobic drug can be entrapped in this nonpolar region.The types of niosomes in practice are proniosomes, aspasomes and deformable niosomes or elastic niosomes.

6.2.3 Proniosomes

Are dry granular product and after hydration they are able to form a noisome suspension. Simply,

Carrier + surfactant = Proniosomes and Proniosomes + water = Niosomes. Aspasomes are prepared using the mixture of acorbyl palmitate, cholesterol and highly charged lipid diacetyl phosphate. Initialy, aspasomes are hydrated with water or aqueous solution and then sonicated to attain the niosomes. Aspasomes are used to improve the transdermal permeation of drugs. Due to its intrinsic antioxidant property, aspasomes have also been used to reduce disorders caused by reactive oxygen species. Deformable niosomes or elastic niosomes are prepared using nonionic surfactants, ethanol and water.They are efficient than conventional niosomes due to their capability to increased penetration efficiency. As they are flexible, their structure allows them to pass through pores that are less than one-tenth of these vesicles [64-75].

6.2.4 Nanoparticles

The lipid nanoparticles are good candidates for transdermal delivery. The size of nanoparticles generally ranges between 10 to 1000 nm. They can be prepared in different sizes and modification in surface polarity is possible in order to improve skin penetration. The nanoparticles include solid lipid nanoparticles (SLN) , nanostructured lipid carriers, lipid drug conjugates and other colloidal drug carrier systems. The reduced size of drug-loaded nanoparticles induces a dramatic increase in the cellular uptake of the nanoparticles. They are similar like nanoemulsions, differing in lipid nature. The lipid used in nanoemulsions is liquid in nature while in case of nanoparticles, it is solid at room temperature. The high melting point glycerides or waxes are examples of lipids used in solid lipid nanoparticles. SLNs can be produced by high pressure homogenization or by the microemulsion technique. During preparation, the drug may be dissolved, entrapped, encapsulated or attached to a nanoparticle matrix to obtain nanoparticles, nanopheres or nanocapsules. The method of preparation decides the nature of final product. The nanocapsules are vesicular systems and drug is confined to a cavity surrounded by a unique polymer membrane. In case of nanospheres, these are matrix systems in which the drug is physically and uniformly dispersed. [76] The polymeric nanoparticles are prepared from biocompatible and biodegradable polymers. The penetration and transport of these systems through the skin depends on the ingredients chemical composition, the encapsulation mechanism influencing the drug release, size of nanoparticles and on the viscosity of the formulations.The polymeric nanoparticles can modify the activity of drugs, delay and control the drug release, and increase the drug adhesivity or its time of permanence in the skin. The nanoparticles are useful as reservoirs to control the permeation of lipophilic drugs through stratum corneum. [77,78].

7. CONCLUSION

It is concluded that the most commonly used transdermal system is the skin patch using various types of technologies. Stratum corneum is the outermost layer of the skin and it is the main barrier layer for permeation of drug in transdermal delivery of drugs. So, to circumvent the barrier properties of stratum corneum and to increase the flux of drug through skin membrane various penetration enhancement techniques are used in transdermal drug delivery system.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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