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Review Article

EFFECT OF CHEMICAL PENETRATION ENHANCERS ON SKIN PERMEATION: A REVIEW

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ABSTRACT
Transdermal drug delivery has attracted considerable attention over the past 2-3 decades in regard of its many potential advantages. Skin penetration enhancers have been used to improve bioavailability and increase the range of drugs to be administered by topical and transdermal route. Therefore, skin penetration enhancers are frequently used in the field of transdermal drug delivery in order to reversibly reduce the barrier function of the stratum corneum, the outermost layer of the skin. The mechanism of action of penetration enhancers are used as an aid in potential clinical applications. Chemical penetration enhancers are present in a large number of transdermal, dermatological, and cosmetic products to aid dermal absorption of curatives and aesthetics. This review presents a critical account of the most commonly used chemical penetration enhancers (fatty acids and surfactants), and some newer classes of chemical enhancers (terpenes, polymers, monoolein, oxazolidinones), with emphasis on their efficacy, mechanism of action, and skin irritation potential. This review also discusses the recently developed methods for the screening and evaluation of chemical penetration enhancers, and addresses the continuing problems in the rational selection of a chemical penetration enhancer for a specific drug to be delivered via the transdermal route.
KEYWORDS: Transdermal Drug Delivery, skin penetration enhancer, stratum corneum, chemical penetration enhancers.

INTRODUCTION

A transdermal drug delivery is a formulation or device that maintains the blood concentration of the drug within the therapeutic window ensuring that drug levels neither fall below the minimum effective concentration nor exceed the minimum toxic dose. This route is recognized as one of the potential route for the local and systemic delivery of drugs. In comparison to conventional pharmaceutical dosage forms, TDDS offer many advantages, such as elimination of first pass metabolism, sustained drug delivery, reduced frequency of administration, reduced side effects and improved patient compliance. In order to permeate and absorb sufficient amount of drug to show the therapeutic effect, permeation should be enhanced. Many approaches such as use of chemical, physical, chemical-chemical, chemical-physical and physical-physical enhancers have been applied for permeation enhancement of drugs[1-3].

Skin Physiology And Drug Permeation

The skin (Fig.1) is the largest organ of the body, its primary function being a permeability barrier to the surrounding milieu. It consists of eccrine and apocrine sweat glands, hair follicles, and sebaceous glands (also referred to as pilosebaceous glands) which play a significant role in the transport of molecules across the skin[4-6]. The outermost layer of the skin, the stratum corneum or horny layer, consists of hexagonal cells, called corneocytes, which are continuously replenished by the slow upward migration of cells produced by the basal layer of the epidermis. It acts as a barrier against the transport of water and xenobiotics[7,8]. Underlying the stratum corneum is the viable epidermis which makes a flat interface with the dead, horny layer, consists of, from top to bottom, the translucent layer (stratum lucidum), the granular layer (stratum granulosum), the spinous or prickle layer (stratum spinosum), and the basal layer (stratum germinativum)[4,5]. The main cells of the viable epidermis are keratinocytes. The top two layers of the viable epidermis, the stratum lucidum and the stratum granulosum, are physiologically very important. Removal of these three epidermal layers results in water loss and an enhancement of skin permeability[7]. The dermis follows the epidermis is a complex structure and consists of cells including fibroblasts, mast cells, endothelial cells, blood cells, and nerve cells. The dermis is rich in blood capillaries, a network of sensory nerves, and a lymphatic network. Therefore, when a topically applied drug molecule reaches the vascularised dermal layer, it becomes available for absorption in to the general circulation[5].

Permeation Enhancers

Permeation enhancers (sorption promoters or accelerants) are used for improving transdermal drug delivery which penetrates into skin to reversibly reduce the barrier resistance. Its mechanisms includes disruption of intercellular lipid and/or keratin domains and tight junctions which results in enhanced drug partitioning into tissue, altered thermodynamic activity/solubility of drug[9].

There are three types of penetration enhancers (Table 1):

1. Drug vehicle based

This method is based on drug selection, vesicles and particles, prodrugs, chemical potential of drug and eutectic 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[10].

2. Physical penetration enhancer

There are numerous physical and electrical method Which are used for penetration enhancement. These include iontophoresis (by a small direct current –approximately 0.5 mA/cm2), 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), phonophoresis (by low frequency ultrasound energy increases lipid fluidity) and photomechanical waves (laser-generated stress waves reported to cause a possible transient permeation of the stratum corneum)[11].

3. Chemical Penetration Enhancers

Chemical penetration enhancers (Table.2) are considered to be the most extensively used technique to enhance a drug's permeation across the skin, leading to increased systemic availability.

Mechanism

Chemical penetration enhancers are believed to work through a combination of mechanisms

- Interact with intracellular proteins embedded in corneocytes to increase transcellular permeation and/or increase the partitioning of the active molecule into the stratum corneum
- Enhancing the paracellular diffusivity through the skin membrane
- Disorganization of intercellular lipids of the skin membrane [12, 13].

Ideal Properties

- Colourless, odourless and tasteless.
- Compatible with most drugs and/or compounds and excipients.
- High chemical and physical stability and pharmacological inertness.
- Non-toxic, non-irritant, non-allergenic and non-phototoxic.
- Work rapidly and the duration of action should be both predictable and reproducible.
- Should work unidirectional.
- Should have no pharmacological activity within the body.
- Should be cosmetically acceptable[14-16].

The most common chemical enhancers and/or enhancer classes are discussed below:

NATURAL PERMEATION ENHANCERS

Terpenes

Terpenes, Fig.2 (A) naturally occurring volatile oils, are considered as less toxic and irritant effects and characterized as Generally Recognized as Safe (GRAS) by the US FDA[17]. They have high percutaneous enhancement ability, reversible effect on the lipids of SC, minimal percutaneous irritancy at low concentrations (1-5%) [18-20]. In recent years, many attempts have been made to investigate the use of terpenes as skin permeation enhancers, including menthol, linalool, limonene, and carvacrol to promote the transdermal transport of drugs, including chiral agents[21]. The mechanism of action of terpenes involves increasing one or more of the following effects: (1) diffusion coefficient, (2) partition coefficient, (3) drug solubility (i.e., increasing the thermodynamic activity of the drug), (4) lipid extraction (i.e., disruption of lipid–protein domain), (5) macroscopic barrier perturbation, and (6) molecular orientation of terpenes molecule within the lipid bilayer. However, the rate and extent of enhancement are dependent upon (1) type and physico-chemical characteristics (such as melting point, solubility) of terpene, (2) concentration of terpene used, (3) absence or presence of cosolvent or enhancer, and (4) concentration of cosolvent or enhancer, if present[22-23].

Dimethyl Isosorbide

Dimethyl sulphoxides (DMSO) is used as a "universal solvent". DMSO alone has been applied topically to treat systemic inflammation. DMSO is needed for optimum enhancement efficacy. DMSO works rapidly as a penetration enhancer - spillage of the material onto the skin can be tasted in the mouth within a second[24].

Urea Derivatives

Urea (NH_2CONH_2) is a naturally occurring odourless and colourless solid substance used as a hydrating agent in dermatology for the treatment of psoriasis, neurodermatitis and other hyperkeratotic skin conditions. The keratolytic properties of urea and its derivatives are used as penetration enhancer. Urea influences the stratum corneum keratinocytes with species-specific percutaneous absorption rates[25, 26].

Azone

Azone increases penetration through stratum corneum by affecting the both lipophilic and hydrophilic route of penetration. Azone by increasing the fluidity of layer and partition in the aqueous region helps in increasing the penetration of hydrophilic drugs [27].

Oxazolidinones

Oxazolidinones are a class of compounds containing 2-oxazolidone as part of the structure. Several oxazolidinones have been synthesized such as 4-benzyloxazolidin-2-one, 4-decyloxazolidin-2-one, 3-acetyl-4-decyloxazolidin-2-one, 3-methyl-4-decyloxazolidin-2-one, 3-methyl-4-benzyloxazolidin-2-one, and 5-decyloxazolidin-2-one and used as chemical penetration enhancers. It is a new class of chemical agents which are odourless and nonstaining in nature and have the potential for use in many cosmetic and personal care product formulations. These are high molecular weight compounds and their structural features are closely related to sphingosine and ceramide lipids which are naturally found in the upper skin layers. The mechanism of action of oxazolidinones may involve the interaction with stratum corneum lipids and can fluidize the bilayer lipids in the stratum corneum, thereby enhancing the skin penetration of various active ingredients[28,29].

Fatty Acids

Oleic acid Fig.2 (C) is a mono-unsaturated fatty acid and is reported to increase the permeation of lipophilic drugs through various mechanisms such as partitioning into lipid bilayers and disrupting their ordered domains, improving drug portioning into the stratum corneum and forming lipohilic complexes with the drugs. Isopropyl myristate is another example of this category. They act by portioning themselves in the ordered lipid domains of the stratum corneum. Ethyl acetate also enhances permeation in the similar manner of sulfoxides and foramides by penetrating in to the stratum corneum and increase the lipid fluidity by disruption of lipid packaging[30-32].

Phospholipids

Phospholipids have been successfully used as permeation enhancers in the form of microemulsions, vesicles and micellar system. They penetrate the surface of stratum corneum where they fuse with the lipid bilayer, thereby enhancing the partitioning of encapsulated drug as well as disruption of ordered bilayer structure[33]. Different phospholipids, in different ways promote drug permeation and affect differently the partitioning of drugs into the lipid bilayer, which explains the differences between phospholipids in promoting the dermal drug delivery. Phospholipids, e.g. fluid-state EPC (L-a-phosphatidylcholine from egg yolk), diffuse into the stratum corneum and enhance dermal and transdermal drug penetration, while many other phospholipids, e.g. gel-state DSPC (distearoylphosphatidyl choline), are not able to do this[34].

Monoolein

Monoolein Fig.2 (B) is a monoglyceride, with a structure similar to oleic acid. Monoolein, a biodegradable polar lipid, is insoluble in water but its molecules self-associate. Monoolein is able to form a bicontinuous cubic liquid crystalline phase that can be used as a drug delivery system. Several studies have suggested that monoolein should be used for topical, rather than transdermal drug delivery. Monoolein has been reported to enhance the skin penetration of several permeants including nitredipine, indomethacin, cyclosporine A, a cyclic undecapeptide and doxorubicin. Its concentration influences its skin penetration enhancing ability. Monoolein concentrations from 5-70% (in propylene glycol formulations) on the topical delivery of cyclosporine A using excised porcine skin, found at a lower concentration of 5%, monoolein could improve only the topical delivery of cyclosporine A, while a 10%
concentration enhanced both topical and transdermal delivery of the model drug. Further
increase in its concentrations from 20% to 70% resulted in an increase in the topical delivery of cyclosporine A, but a decrease in the transdermal delivery of drug. Monoolein may function by disruption of the lamellar structure of the bilayer in the stratum corneum, which leads to increased lipid fluidity in the stratum corneum. However, it may remove skin ceramides and solubilize lipophilic compounds in the skin. Although monoolein is non-toxic but it produces skin irritation in some cases[35].

Surfactants

Surfactants generally consist of a lipophilic alkyl or aryl chain together with a hydrophilic head group. They can be classified into four main categories according to the presence of formally charged groups in the head; anionic (e.g. sodium lauryl sulfate), cationic (e.g. cetyltrimethyl ammonium bromide), nonionic (e.g. polyoxyethylene sorbitan monopalmitate) and amphoteric (e.g. N-

dodecyl-N, N-dimethylbetaine). They play an important role in many products, including, pharmaceuticals, cosmetics, and food formulations. They have long been used as detergents, solubilizers, wetting agents, adhesives, personal products, emulsifiers and suspending agents. Surface active agents act by adsorption at interfaces and thus interact with biological membranes contributing to the overall penetration enhancements of the compounds. These include anionic, cationic, zwetterionic and non-ionic surfactants. Cationic are more destructive to skin and produce greater flux than non-ionic surfactants[36-38].

CONCLUSION

Generally, commercial skin products can be classified into two classes, topical and transdermal preparations. A topical application is intend to confine the pharmacological effects or other effects of active ingredients to the surface of the skin or within the skin, which are available in several dosage forms, such as creams, emulsions, lotions and gels. It has been well known that topical products usually contain many components, including chemical enhancers as excipients. A transdermal application is intended for systemic effects. To achieve therapeutically effective dose of the drug through the skin, a chemical penetration enhancer is a major tool. Chemical penetration enhancer is used to enhance the delivery of therapeutically effective dose of the drug through the skin. In the pharmaceutical science literature, chemical enhancers have been used to enhance skin permeability towards stratum corneum and they also penetrate into the deeper layers of the skin to viable epidermal cells and induce skin irritation responses. More than 300 chemical enhancers have been discovered, but only few enhancers (e. g. terpenes) have been classified by FDA as 'safe' for use in the products. The nonspecific activity of chemical enhancers towards the skin layers has lead to the development of mixtures of chemical penetration enhancers, which are called synergistic combinations of penetration enhancers or SCOPE formulations. The binary mixtures of chemical enhancers not only significantly increase the skin penetration of the drug, but also increase the safety in comparison to the single enhancers.

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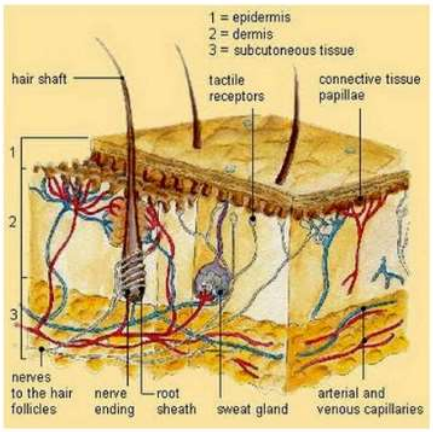


Fig.1: Cross Section of skin

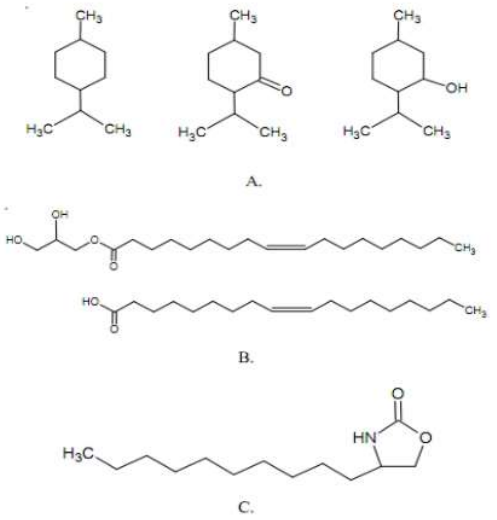


Fig. 2: Chemical structures of some skin chemical penetration enhancers. A. monocyclic terpenes: p-menthane (left), menthone (middle), and menthol (right); B. Monooelin (top) in comparison with oleic acid (bottom); C. 4-decyloxazolidin-2-one.

Table.1: Effect of Permeation Enhancers on different Formulations.

Sr.No	Drug Vehicles based	Chemical penetration Enhancers used	Physical Methods
1.	Drug Selection	Terpenes	Iontophoresis
2.	Prodrugs and Ion pairs	Dimethyl Sulfoxide	Magnetophoresis
3.	Chemical Potential of drug	Urea	Electroporation
4.	Complexes	Azone	Ultrasound
5.	Eutectic System	Pyrolidine	Thermophoresis
6.	Vesicles and particles	Fatty Acids	Needleless Injection
7.		Oxazolidinones	Skin Abrasion
8.		Monoolein	Radio Frequency
9.		Phospholipids	Application of Pressure

Table. 2: Types of chemical penetration enhancers classified by functional groups and chemical structures.

Types	Examples
Terpenes	limonene, nerolidol, farnesol, carvone, menthone
Azone and Derivatives	Azone (laurocapram; 1-dodecylazacycloheptan-2-one), 1-alkyl- or 1-alkenylazacycloalkanones
Urea and Derivatives	urea, 1-dodecylurea, 1-dodecyl-3-methylurea,1-dodecyl-3-methylthiourea
Oxazolidinones	4-decyloxazolidin-2-one, 3-acetyl-4-decyloxazolidin-2-one
Monoolein	Monoolein
Fatty Acids	alkanoic acids, oleic acid, lauric acid, capric acid
Surfactants	sorbitan monopalmitate, sorbitan trioleate, cetyl trimethyl ammonium bromide, sodium lauryl sulfate
Sulfoxides	dimethylsulfoxide, dimethylacetamide, dimethylformamide

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