

Penetration Enhancement Techniques

Shikha Baghel Chauhan*

Amity Institute of Pharmacy, Amity University, Noida, Uttar Pradesh, India

Abstract

Penetration Enhancers have vast potential and if utilized thoroughly, can be beneficial route in the drug delivery. Penetration Enhancers facilitates the drug delivery in various ways. They are therefore also referred as sorption enhancers or accelerants. This review focusses on the various enhancement techniques which are widely used to increase the bioavailability of the drugs. This review explores the various penetration enhancers with their mechanism of action and their roles in enhancement techniques. One of the reasons why the Transdermal drug delivery has not been successful compared to other delivery system, is the impervious nature of the versatile skin. It has been reported that individual penetration enhancer are not able to bring that effect which is achieved by the combination of penetration enhancer or mixture of penetration enhancer. Different penetration enhancers act at different site of action and have different mechanism of action ranging from altering metabolic activity within the skin, or exerting an influence on the thermodynamic activity of the drug in its vehicle. The major limitation in transdermal drug delivery is the diffusion of drug molecules to cross, one of the most versatile barriers of skin. A number of skin penetrations enhancers have been investigated and explored for skin penetration enhancement. Further, developments and initiatives are required to evaluate the mechanism of enhancement techniques. A thorough understanding of this penetration enhancer has been discussed and future implications explored.

Keywords: Transdermal; Permeation enhancer; Mechanism; Skin penetration enhancers; Transdermal drug delivery; Penetration enhancement techniques

Introduction

The skin is a continuously self-renewing organ that covers the surface of the body and separates it from the outside world with which it connects in a dynamic way. It provides protection against external agents such as mechanical and chemical insults, heat, infections, water, and electromagnetic radiation [1].

The composition and structure of skin offers maximum resistance for permeation of drugs to reach systemic circulation. This is a boon on one side, as it serves as a great protection against various pathogens, virus, diseases etc. On the other hand this nature of skin serves as a hurdle for the useful key drugs required for treatment. Hereby, comes the role of penetration Enhancers and Enhancement techniques which facilitates the entry of these chemical moieties into the skin by altering the nature of skin or by disrupting the permeability of skin or by reducing the diffusional resistance of the skin. Penetration Enhancers and penetration enhancement techniques allows drugs and other chemical moiety selectively. This selection depends on various factors such as extent of lipophilicity and hydrophilicity of the drugs. The more the lipophilicity, the better the absorption [2].

Ideal Penetration Enhancers should be colourless, odourless and tasteless, compatible with the drugs, physically and chemically stable and inert, nontoxic, and nonirritant in nature, fast acting and reproducible in nature, should not have any pharmacological activity, enhance the appealability of the skin and should not form any complex with the drug [3].

Transdermal Penetration Routes

Permeation takes place by diffusion through [4,5]:

1. Transdermal permeation;
2. Intercellular permeation;
3. Permeation through hair follicles, sweat glands and sebaceous glands.

The various methods developed for enhancing penetration across the stratum corneum are broadly classified into following enhancement techniques [4]:

1. Chemical enhancement;
2. Physical enhancement;
3. Biochemical enhancement;
4. Supersaturation enhancement;
5. Bioconvertible prodrug-Prodrug approach.

Chemical enhancement

Chemical Penetration Enhancers-Chemical Penetration Enhancers (CPEs) are vastly present in huge numbers to facilitate the penetration of drugs in transdermal, demagogical and cosmetic products [6].

Water: Water is the best reported penetration enhancer. Hydrated skin better absorbs the drug molecules since it increases the flux required for penetration [7]. Better the hydration better will be rate of penetration of the drug molecules. It is the simplest technique for improving the penetration of drugs through Transdermal patches [6].

Mechanism of action: They exert their effect by using a range of mechanisms [8]: 1) Disrupting the lipid bilayer structure in the stratum corneum (SC) and thereby increasing the drug's diffusion coefficient, extracting lipids from the SC, 2) Altering the solvent nature of the SC and consequently modifying the drug partitioning coefficient, acting

*Corresponding author: Shikha Baghel Chauhan, Assistant Professor, Amity Institute of Pharmacy, Amity University, Noida, Uttar Pradesh, India, Tel: 0120 244 5252; E-mail: schauhan@amity.edu; shikha.pharma@gmail.com

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on intracellular keratin, etc. 3) Ionic surfactants and DMSO also interact with the keratin structure in the corneocytes. This opens up the tight protein structure and leads to an increased diffusion coefficient through the corneocytes, being however not of great importance as the intercellular route, and not the intracellular route, is the major penetration pathway through the SC.

The enhancer act by altering one of three pathways. The key to altering the polar pathway is to cause protein conformational change or solvent swelling. The fatty acid enhancers increased the fluidity of the lipid protein portion of the stratum corneum. Some enhancers act on both polar and nonpolar pathway by altering the multilaminar pathway for penetration. Enhancers can increase the drug diffusivity through skin proteins. The type of enhancer employed has a significant impact on the design and development of the product.

A useful way to consider factors affecting drug permeation rate through the stratum corneum is via the simple equation given below for steady state flux,

If we plot the cumulative mass of diffusant, m , passing per unit area through the membrane, at long time the graph approaches linearity and its slope yields the steady flux.

$$\frac{dm}{dt} = D \frac{C_0 - K}{h} \quad (1)$$

Where C_0 is the constant concentration of drug in donor solution, K is the partition coefficient of the solute between the membrane and the bathing solution, D is the diffusion coefficient and h is thickness of membrane. From the above equation, we deduce the ideal properties of a molecule that would penetrate stratum corneum well (9).

These are:

- Low molecular mass, preferably less than 600 Da, when D tends to be high.
- Adequate solubility in oil and water so that membrane concentration gradient may be high.
- High but balanced (optimal) K (if too large, may inhibit clearance by viable tissue).
- Low melting point, correlating with good solubility as predicted by ideal solubility theory.

Chemical enhancers can be categorized into different groups on the basis of their chemical structure. Solvents like alcohols and polyols mainly increase drug's solubility in the SC and improve partitioning of the drug into the SC. Some solvents (dimethyl sulphoxide (DMSO), ethanol) may extract lipids, making the SC more permeable as they form aqueous channels. Laurocapram (Azone) and oleic acid are examples of chemical enhancers that can insert themselves into the SC lipid bilayer structures and disrupt the packing of the lipids. The result of this is that the lipid structure of the SC becomes more fluid and the diffusion coefficient of the permeant is increased. Despite being very effective in enhancing drug permeation through the skin, many chemical penetration enhancers have a limited use in topical and transdermal drug delivery systems because they can cause skin irritation [9,10].

Physical enhancement techniques

Iontophoresis: In this penetration enhancement technique, permeation is enhanced with the application of electrical current. A cell like structure is designed; whereby two electrodes, anode and cathode are set up. The whole set up is installed on the skin. Due to force exerted by electrical current drug molecules are forced to permeate inside the

skin [11,12]. There are various mechanisms which have been anticipated for faster permeation.

i) The drug is pushed into the various layers of skin by anode cathode charge development. Anionic charge moves to cathode, whereby cationic charge moves to anode [13].

ii) The electric current disrupts the protective nature of skin [14].

iii) It is anticipated that this technique facilitates the accumulation of water by electroosmosis, which results in hydration of skin and drug penetration is increased due to better hydrated condition of skin [15].

Electroporation: In this method, drug penetration enhancement is achieved by the application of pulses in high voltage (50-1000 V) for short duration (microseconds and milliseconds) to the skin. Due to pulses exposed, transient pores are formed whereby drug molecules can also penetrate and hence bioavailability increases. The drug molecules actually diffuse through the channels widened up [16]. Larger macromolecules have also been delivered by electroporation, including insulin, [17] vaccines, [18] oligonucleotides [19], and micro particles [20]. A few model compounds such as calcein [21] and LHRH [22] drugs have also explored.

Sonophoresis: Another technique beside electroporation attempting to overcome the challenges of transdermal drug delivery involves the usage of high or low frequency ultrasound waves. The enhancement may result from enhanced diffusion due to ultrasound-induced skin alteration and/or from forced convection. Tang et al have a theory describing the transdermal transport of hydrophilic permeants in the presence of ultrasound.

Conical microscopy indicates that cavitations occur in the keratinocytes of the stratum corneum upon ultrasound exposure [23]. Recent studies have shown that ultrasound can increase up to 5,000 times the ability of protein the size of insulin to penetrate the skin. Using a transdermal patch design in conjunction with ultrasound may provide an improved method for Insulin delivery [24,25].

Photomechanical waves: Photomechanical waves are also known as laser generated stress waves. Photomechanical waves are the pressure pulses produced by ablation of a material target (polystyrene) by Q-switched or a mode-locked laser. The application of pressure waves does not cause any pain or discomfort and the barrier function of the SC always recovers [26]. The largest molecule that has been reported to be delivered through the rat skin to date has a molecular weight of 40,000 Da. Suggestions have been made that many clinically important proteins such as insulin (6000 Da) and hemoglobin (48000 Da) are within or close to the delivery capability range of PW's. However; this relatively new technique does not yet seem to have produced any human clinical data [27,28].

Electret enhances TDDS: Electret is an electrically charged Teflon[®] disk that carries semi-permanent electric charge. It is characterized by the surface potential in volts [29]. These provide surface potentials from 500 to 3000 V, easily measurable using an electret reader. Electrets and the electret readers used in this study are commercially available under the brand name E-PERM[®] (Rad Elec Inc., Frederick, MD, U.S.A.). The active surface of the electret is about 12 cm². These are widely used as components of electret ion chambers used for measuring radon and radiation. Electret was found to enhance the penetration of hydrophilic drugs (but not lipophilic drugs) across the skin. However, the electret effect disappears when moisture content in the formulation increases. The electrets seem to work well with the topical bases which do not have moisture in them. The surface voltage of electret was not affected

significantly by the presence of white petroleum jelly coating on the E-PERM[®] electrets. It is also possible to use a thin layer of removable uncharged Teflon[®] to cover the surface of the electret. This allows electric field to go through and at the same time protects the electret surface from getting contaminated. Cui et al. have reported the effect of electret on the skin permeability of methyl salicylate [30,31]

Microfabrication microneedles technology: The microfabricated microneedles technology employs micron-sized needles made from silicon [32]. Microneedles have been fabricated with different range of size, shape and materials. These microneedle arrays after insertion into the skin create conduits for transport of drug across the stratum corneum. Microneedles inserted into the skin of human subjects were reported as painless. Drug delivery by microneedle increase skin permeability for a broad range of molecules and nanoparticles [33,34].

Macroflux: The system incorporates a titanium microprojection array that creates superficial pathway through the skin barrier layer to allow transportation of therapeutic proteins and vaccines or access to the interstitial fluids for sampling. The microcapillaries for systemic distribution absorb the drug. The rate of absorption is promoted by the high local drug concentration around the microprojections and the large surface area provided by the patch array. Three types of Macroflux[®] have been designed and tested in preclinical studies. They include, Dry-Coated Macroflux[®] System for short duration administration that consists of a drug coated microprojection array adhered to a flexible polymeric adhesive backing [35].

Jet propelled particles: The use of compressed gas to force solid drug particle through a convergent divergent nozzle was reported by Bellhouse et al. using compressed helium. High-velocity powder injection is a promising new drug-delivery technique that provides needle and pain-free delivery of traditional drugs, drugs from biotechnology such as proteins, peptides, and oligonucleotides as well as traditional and genetic vaccines. The energy of a transient helium gas jet accelerates fine drug particles of 20-100 μm diameter to high velocities and delivers them into skin or mucosal sites. Particle velocity is controlled within the device by three parameters namely nozzle geometry, membrane burst strength and gas pressure [36]. Preclinical and clinical results that best characterize the technology and introduce its potential as a drug-delivery platform.

Jet propelled particle device has been reported to successfully deliver testosterone, lidocaine hydrochloride, and macromolecules such as calcitonin and insulin [28].

Heat enhanced transdermal drug delivery: Heat influences blood vessels wall permeability, which in turn increases total fluid circulation. Due to increase in total fluid, permeability of the drug molecules into the systemic circulation is enhanced. Heat may also cause changes in physiochemical properties of patches. Other factors like sweating and hydration of skin are also altered, which increases the penetration of drugs [37].

Heat is expected to enhance the transdermal delivery of various drugs by increasing skin permeability, body fluid circulation, blood vessel wall permeability, rate-limiting membrane permeability, and drug solubility [37]. According to Kligman [38], diffusion through the skin, as elsewhere, is a temperature dependent process, so raising the skin temperature should add thermodynamic drive. Heat is known to increase the kinetic energy of the drug molecules and the proteins, lipids, and carbohydrates in the cell membrane. Heating prior to or during topical application of a drug will dilate penetration pathways in the skin, increase kinetic energy and the movement of particles in

the treated area, and facilitate drug absorption. Heating the skin after the topical application of a drug will increase drug absorption into the vascular network, enhancing the systemic delivery but decreasing the local delivery as the drug molecules are carried away from the local delivery site.

Needleless injection: One of the best techniques, since it does not involve any pain and discomfort to the patient. It is highly sophisticated technique whereby liquid and solid particles are bombarded at supersonic speed into the skin [39]. The technique utilizes compressed gases such as Helium or nitrogen through narrow nozzle along with the drug molecules in a jet flow [40]. But the problems associated with this technique are high development cost for dosage form development and to control the device once initiated due to variability in skin permeability [41].

Magnetophoresis: In this enhancement technique, magnetic field is utilized to facilitate the penetration of drug molecules in the skin. It alters the skin structure, thereby changing its protective properties [42]. Magnetoliposomes are magnetic nanoparticles coated by a phospholipid bilayer used for targeted drug delivery systems, magnetic resonance imaging biomarkers for cancer diagnosis, and thermal cancer therapy [43]. Magnetophoresis is a novel approach in enhancing drug delivery across biological barriers. The influence of magnetic field strength on diffusion flux was determined and was found to increase with increasing applied field strength [42].

Mechanical perturbation: Microstructured Transdermal Systems enables the disruption of the outermost layer of the skin, the stratum corneum, without causing pain. MTS expands the range of drugs that can be delivered transdermally and potentially reduces variation in transdermal drug delivery caused by different skin types and application sites. It is suited for vaccines, protein or peptide based drugs [44].

Laser ablation: The use of lasers to remove the stratum corneum barrier by controlled ablation has also been investigated as a means of enhancing topical drug delivery [45]. This method involves direct and controlled exposure of a laser beam to the skin which results in the ablation of the stratum corneum without significantly damaging the underlying epidermis. Removal of the stratum corneum using this method has been shown to enhance the delivery of lipophilic and hydrophilic drugs. It has been also reported that laser ablation of stratum corneum enhanced the permeation of both hydrocortisone and interferon [46].

Biochemical enhancement

Biochemical enhancement is also another technique employed for molecules like like 11-amino acid synthetic peptide derived by phage display screening [47] and a polyarginine heptamer which is attached to drug by making it prodrug [48]. Another class example is magainin [49] which is a natural pore former peptide. This biochemical enhancer is great tool and can be utilized for transdermal drug penetration enhancement.

Supersaturation enhancement

In this enhancement technique, increased penetration is achieved by creating concentration gradient according to the fick's law. The technique involves development and utilization of thermodynamic potential of the drug. The concentration gradient ($C_o - C_i$) in Fick's law: $\{J = KD/h (C_o - C_i)\}$.

The methods used to develop supersaturated systems are removal of excess solvents, reaction of compounds for decreasing the solubility,

simultaneous heating and cooling, addition of substances which can decrease the solubility and results in supersaturation [50,51].

Bioconvertable prodrug-prodrug approach

Prodrugs refer to the inactive form of the drug, which need to be processed by metabolism before converting to an active form. The inactive form is more lipophilic than the active form [52].

Various drugs have been converted and delivered through pro drug approach for example estradiol and other hormonal treatments. It has been found that the drug release rate of estradiol is dependent on the chain length of the ester group at the 17th position [53].

Prodrugs of ketorolac have high lipophilicity and therefore the increased penetration is achieved by Transdermal Drug Delivery [54]. The prodrug approach has also been used for protein and peptide drug delivery (Tables 1 and 2) [55].

Conclusion

The efficacy of the penetration enhancer depends on the way in which it is able to alter the lipid channels and create the pathways to reach systemic circulation. The partition coefficient is also very important in determining the degree of penetration. The penetrants having high lipid solubility are able to provide more enhancements in bioavailability. It is also found in the literature that the concentration of penetrant also plays a very critical role. As the concentration of the

penetration enhancers increases, the drug molecule entry is facilitated and henceforth, the drug bioavailability increases. Since the transdermal drug delivery system is advanced targeted drug delivery system, if by utilizing such enhancement techniques and using penetration enhancers in formulation development, definitely increased concentration drug can be achieved in systemic circulation, thereby making transdermal drug delivery more effective and successful.

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S. No.	Chemical Classification	Enhancer
1	Alcohols	Ethanol, Isopropyl alcohol
2	Amides	Azone
3	Esters	Ethyl acetate, Oleyl acetate, Isopropyl myristate, propylene glycol monocaprylate
4	Fatty acids	Lauric acid, Linoleic acid, oleic acid
5	Glycols	Propylene glycol
6	Pyrrolidone	N-methyl-2-pyrrolidones, 2-pyrrolidone
7	sulfoxides	Dimethyl sulphoxide
8	Surfactants	Anionic surfactants, Sodium lauryl sulphate, Cationic surfactants Alkylpyridinium halide
9	Terpenes	Cineole, Eugenol, D-Limonene
10	Urea	Carbamide
11	Miscellaneous	Cyclodextrins, Water, Vitamin E, Phospholipids

Table 1: Examples of penetration enhancers investigated [6].

Physical Penetration Enhancement Techniques	
a) Electrically Based	Iontophoresis
	Electroporation
	Sonophoresis
	Photomechanical waves
	Electret
b) Structured Based	Microneedle
	Macroflux
c) Velocity Based	Power Jet
	Needleless Injection
d) Others	Heat
	Magnetophoresis
	Skin perturbation
	Laser Ablation

Table 2: Physical enhancement techniques.

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