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Potential Enhancers for Transdermal Drug Delivery: A Review

Abid Hussain[1], Gul Majid Khan[2], Abdul Wahab[3], Muhammad Akhlaq[4], Saif ur Rahman[1], Hamza Altaf[1], Naheed Akhtar[1] and Muhammad Imran Qayyum[1]

[1]Department of Pharmacy, University of Poonch, Rawala Kot Azad Kashmir, Pakistsan.

[2]Department of Pharmacy, Quaid-E- Azam University, Islamabad, Pakistan.

[3]Department of Pharmacy, Kohat University of Science and Technology, Kohat, KPK, Pakistan.

[4]Faculty of Pharmacy, Gomal University, D.I.Khan, Pakistan.

Email: abidhussainkk@gmail.com

Abstract – Transdermal drug delivery system (TDDS) aims to deliver the therapeutic moiety via the skin into the systemic circulation for its therapeutic effect. The transdermal route has been recognized as one of the highly potential routes of systemic drug delivery and provides the advantage of avoidance of the first-pass effect, ease of use and withdrawal in case of side effects, and better patient compliance. However, due to resistance of this route is the difficulty of penetration of drug through the skin. Studies have been carried out to select safe and suitable penetration enhancers to promote the percutaneous absorption of a number of drugs. The present review contains the different penetration enhancers; thus, it will help in the selection of appropriate enhancers for increasing the permeation of poorly absorbed drugs through skin.

Keywords – Transdermal drug delivery, Skin, Stratum corneum, First pass effect, Percutaneous absorption; Penetration enhancer

1. Introduction

The skin is the largest organ of the body covering the entire body. It makes up about 16 % of the total body weight with a surface area of 1.8 m^2. For a long period of time the skin was considered as an impervious membrane, thus preventing any sort of movement of substances into the body. Due to this reason the skin was not studied as a potential route of the drug administration for a long period of time. Later on it was found that substances with a specific set of properties can be transported across the skin. However due to the natural barrier functions of the skin it must be accepted that only few substances are suitable candidates for the conventional TDDS. Many substances will be absorbed through the skin, but in such a small concentrations that their level in the blood will never rise to the concentration required for the therapeutic activity. Many other substances will not be absorbed at all. Percutaneous absorption involves the passage of the drug molecule from the skin surface into the stratum corneum under the influence of a concentration gradient and its subsequent diffusion through the stratum corneum and underlying epidermis, through the dermis, and into the blood circulation. The skin behaves as a passive barrier to the penetrant molecule. The stratum corneum provides the greatest resistance to penetration, and it is the rate-limiting step in percutaneous absorption. Penetration enhancers (or absorption promoters) are the substances that facilitate the absorption of penetrant through the skin by temporarily diminishing the impermeability of the skin. Several scientists are engaged in transdermal permeation studies using various enhancers for several drug moieties. This review discusses a few important permeation enhancers used in transdermal drug delivery.

Ideal characteristics of enhancers

An ideal penetration enhancer should have following properties [1].

- The effect of enhancer on the skin should be reversible, and it should not damage the viable cells.
- It should be pharmacologically inert, non-toxic, non-allergenic and non-irritating.
- It should be compatible with the drug and other additives.
- It should show their effect rapidly; with predictable and reproducible duration of effect.
- It should have unidirectional enhancing effect; allowing the drug molecule to pass through the skin while preventing the loss of endogenous materials like body fluids, electrolytes etc.
- It should be economical.

No single penetration enhancer possesses all these properties; however some penetration enhancers may possesses some of the above attributes [2].

Mechanism of penetration of enhancers [1]

The penetration enhancers may show their effect any one or combination of the following mechanisms.

- By disrupting the structure of *stratum corneum* lipids.
- By interacting with intercellular proteins.
- By improving drug partitioning, co-enhancer or solvent into the *stratum corneum*.

The chemical enhancers show their enhancing effect by bringing alterations in, at least any one three pathways. The polar pathways are altered by solvent swelling or conformational changes in proteins. The fatty acids show their effect by increasing the fluidity of lipid protein portion

of the *stratum corneum*. Some enhancers act on both polar and pathways by altering the multilaminate penetration pathway.

The following equation for the penetration rate (flux) explains the factors which could affect the drug permeation rate.

$$dm/dt = D\ C_o\ K\ /h$$

Where;

dm/dt represents steady state flux

C0 is the constant concentration of the drug in the donor solution

D is diffusion coefficient

h is membrane thickness

K is the partition coefficient of the permeant between the membrane and the bathing solution.

It is clear from the above equation that following factors may affect the rate of drug permeation across the skin.

- Molecular mass of the permeant, preferably less than 600 Da.
- Solubility of drug molecule in oil and water which determines its membrane concentration gradient. Adequate oil and water solubility develops high membrane concentration gradient.
- Melting point; as low melting point correlates with good solubility of drug as described by ideal solubility theory.
- Site of application; as the thickness of the membrane varies throughout the body. The sites with less skin thickness are preferred for more permeation.
- The value of *K;* It should be high (but balanced) for good permeation as if it is too large it may inhibit clearance by viable tissues.

- **Methods for Enhancing Transdermal Drug Delivery**

In last two decades the barrier properties of the skin have been reduced by a number of ways. These may be of two types; active method and passive methods.

❖ **Active methods for enhancing transdermal drug delivery**

Active transdermal delivery enhancing methods increase the transdermal delivery by using an external energy as a driving force. Active methods make possible the permeation of larger molecules which can't be permeated otherwise.

Various active methods used for enhancing transdermal delivery are discussed here below;

i. Iontophoresis: Iontophoresis utilizes electrical potential as driving force for permeation of ionizable drug molecules through the skin. In iotophoresis a small electric current, usually 0.5 mA/cm2, is applied either directly to the skin or through the dosage from [3].

The drug permeation is caused by any one or combination of following mechanisms.

- Electro-repulsion (for similar charged solutes)
- Electro-osmosis (for uncharged solutes)
- Electro-perturbation (for both charged and uncharged solutes)

Iontophoretic techniques may vary in electrode type, current intensity, type of permeant, pH of the system and competitive ion effect [3].

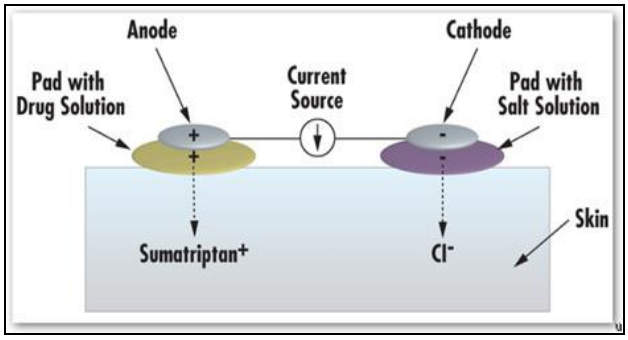

Figure 1. Diagrammatic representation of Iontophoresis with modification [4]

ii. Eletroporation: In electroporation the transdermal delivery of the drug molecule is increased by the application of a high volatage (100 volts) in the form of direct currect (DC). This high voltage produces transient pores in the skin through which macromolecules can pass to the intercellular spaces by combination of diffusion and local and electrophoretic mechanism [5].

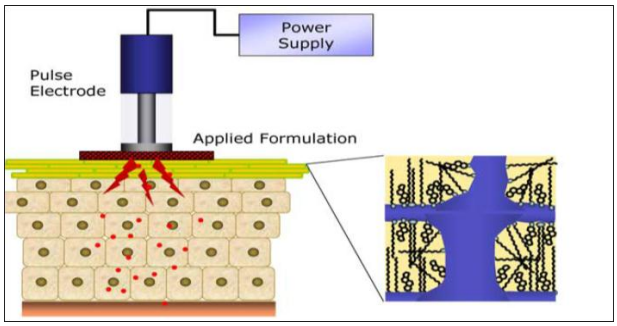

Figure 2. Diagrammatic presentation of Electroporation [5]

iii. Sonophoresis: Sonophoresis, Phonophoresis or Ultr-Phonophoresis are used alternatively for this active transdermal delivery enhancing method. In this method ultrasound, (20 KHz-16 MHz) is used as a driving for to increase the permeation of drug molecules through the skin [6]. In this method the drug is mixed with a coupling agent in the form of gel, cream or ointment. The coupling agent acts as a medium for the transfer of phonophoretic energy from the device to the skin [7]. Sonophoresis causes disruption of *stratum corneum* by cavitation, microscreening and heat sensitization [8]. High frequency ultrasound in the range 1-16 MHz is less effective than low frequency ultrasound in the range 20-100 KHz.

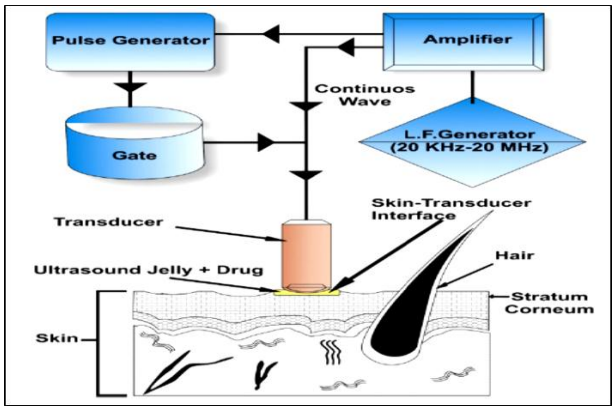

Figure 3. Diagramatic presentation of Sonophoresis

iv. Microneedles: Micrneedles technique may also be called as microscopic projection. As the name indiactes the device contains microprojections which are arranged in array. These microscopic prejections are 10-100 µm in length and 10- 50 µm in width. These microneedles are made up of cilicone and have very shorp tip (Radius of curveture <1 µm). When the device is applied to the skin the microneedles produce micropores which are too larger to allow the drug molecules to pass through them but are to small to cause pain [9].

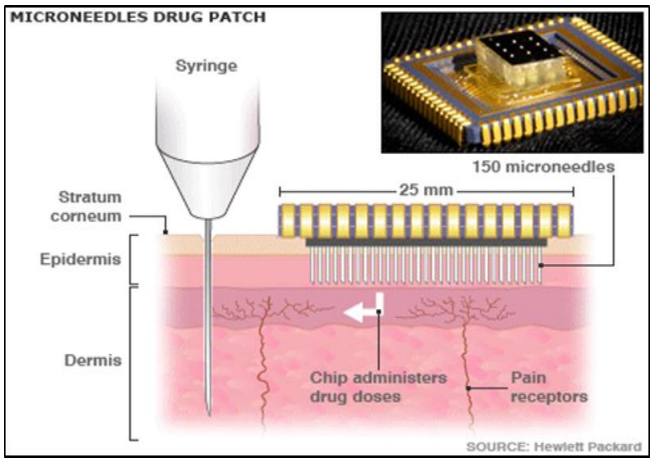

Figure 4. Microneedles based drug patch

v. Magnatophoresis: Magnatophoresis is an active transdermal delivery enhancing method which utilizes the magnetic field as a driving force. This technique can be used for the permeation of diamagnetic molecules. This method has been implemented for the transdermal delivery of benzoic acid. The diffusion flux is in direct proportion with intensity of the applied magnetic field [10].

vi. Skin abrasion: In this technique the transdermal drug delivery is facilitated by producing micro channels in the skin by removal of upper layers of the skin. Special type of devices is used for this purpose. Microderm abrasion device (developed by Med Pharm Ltd., Charbury, UK) is an example of such devices. This technique has increased the permeation of angiotensin by 100 folds as compare to the untreated human skin [11].

vii. Laser Radiations: This technique involves the direct exposure of skin to a controlled beam of Laser radiations which removes *stratum corneum* without damaging the underlined epidermis. The transdermal delivery of lipophilic and hydrophilic drug molecules can be increased by this technique [12].

viii. Thermoporesis: In this technique the skin permeability is increased by increasing the skin surface temperature. First of all Blank *et al.* [13] reported the effect of elevated temperature on the transdermal permeation in 1967. It has been demonstrated that every 7-8°C rise in temperature increases the permeability by 2-3 folds [14]. The following mechanisms may be involved in increasing the skin permeability in thermophoresis technique;

- Increased lipid fluidity which in turn increases drug diffusivity in vehicle and in the skin as well [15].
- Vasodilatation of the subcutaneous blood vessels [16].

It has been reported that an exposure to low (freezing) temperature may reduce the barrier function of the skin [17]. However, still low temperature hasn't been implemented practically as transdermal enhancing technique.

ix. Radio-frequency: This technique involves the exposure of skin to high frequency alternating current (~100 kHz) which produces microscopic passages in the *stratum corneum* by a process called cell ablation. The drug delivery rate is influenced by the number and depth of these microchannels produced. It has been demonstrated from *in vivo* studies that plasma level of granisetron HCl after 12 hours was 30 times greater when exposed to radio frequency than the level recorded for untreated skin after 24 hours [18]. In the same research permeability of diclofenac through the skin was also observed [18].

❖ Passive methods for enhancing transdermal drug delivery

In passive transdermal delivery enhancing methods the barrier properties are not fundamentally altered and a limited amount of drug can be delivered. These methods include;

- The use of supersaturated systems [19].
- The use of chemical penetration enhancers [20].
- Prodrugs or using metabolic approaches [21].
- Liposomes and such other vesicles [22].

Chemical penetration enhancers (CPE)

Permeation enhancers increase the skin permeability by reversibly damaging or altering the physicochemical nature of the *stratum corneum* to reduce its diffusional resistance. Some drugs have inherent capacity to permeate the skin without chemical enhancers. However when this is not case, chemical permeation enhancers are useful in transdermal drug delivery. Chemical penetration enhancers are now most desirably used as transdermal delivery enhancing method. Chemical penetration enhancers interact with the constituents of the skin and alter the barrier functions of the skin reversibly [20].

More than 275 chemical penetration enhancers have been identified and used in various researches. The major chemical penetration enhancers are given here below;

Terpenes and Essential Oils

Terpenes and terpenoids are usually the constituents of volatile oil. Their chemical structure consists of repeated isoprene (C_5H_8) units and is classified according to the number of isoprene units: Monoterpenes have two isoprene units (C_{10}), sesquiterpenes have three (C_{15}), and diterpenes have four (C_{20}). Terpenes may also be classified as acyclic/linear, monocyclic, and bicyclic. The effect of three essential oils (eucalyptus, peppermint, turpentine oil) on the permeation of 5-fluorouracil (5-FU) were studied using excised rat skin. Although all three oils enhanced the permeation of drug, their effect was less than that of azone. Eucalyptus oil was found to be the most active, causing a 60-fold increase, while peppermint and turpentine oil showed 48- and 28-fold increases, respectively. Mode of action of these enhancers may be due to a combined process of partition and diffusion, the latter being dominant [23]. Some cyclic terpenes have also been investigated as penetration enhancers. Cineole, d-limonene, and a-pinene were studied

using human cadaver skin for their absorption-enhancing effect on two neuroleptic drugs, chlorpromazine (CPZ) and haloperidol [24]. None of the three improved the penetration profile of CPZ; d-limonene even reduced its transdermal permeation. Permeation of haloperidol was increased by both cineole and d-limonene; a-pinene provided no change in its permeation profile. Coapplication of terpenes (1,8-cineole, menthone, limonene, nerolidol) with 5-FU, both at saturation, in a propylene glycol (PG)/water cosolvent system increased drug flux significantly [25]. Terpene activity depended on PG content, with maximum flux obtained with formulations containing 80% PG. A dual mechanism of permeation was proposed, one due to increased lipid disruption in the stratum corneum by terpenes and the second due to the increased drug partitioning contributed by the high PG content.

Alcohols, Glycols and Glycerides

Ethanol is the most commonly used alcohol as a transdermal penetration enhancer. It increases the permeation of ketoprofen from a gel-spray formulation [26] and triethanolamine salicylate from a hydrophilic emulsion base [27]. It also acts as a vehicle for menthol in increasing the penetration of methyl paraben [28]. PG solvates the keratin of the stratum corneum, occupying the hydrogen bonding sites. When it is used in combination with azone, large amounts of glycol enter the tissue and promote intracellular diffusion of drugs [29]. Short-chain glycerides are also effective as permeation enhancers (e.g., TCP). For instance, glycerin tricaprylate (caprylic acid triglyceride) in combination with ethanol is used as a solvent system [30, 31]. TCP is an excellent hydrophobic vehicle and promoted the permeability of tegafur combined with ethanol [32]. Glyceryl monocaprylate enhanced the partitioning of papaverine across hairless rat skins [33]. Sefsol 318, a medium-chain glyceride, increased the permeation of papaverine hydrochloride by almost 820 times by increasing the fluidity of the lipoidal membrane of the stratum corneum [34].

Fatty Acids and Esters

A large number of fatty acids and their esters have been used as permeation enhancers. A general trend has been seen that unsaturated fatty acids are more effective in enhancing percutaneous absorption of drugs than their saturated counterparts. Chi et al. [35] reported an increase of 6.5-fold to 17.5-fold in the permeation rate of flurbiprofen through rat skin by unsaturated fatty acids, while no significant increase was observed with saturated fatty acids. Moreover, they have a greater enhancing effect on lipophilic drugs.

References

[1] T. F. Lizelle, G. Minja, D. P. Jeanetta and H. H. Josias, "Transdermal Drug Delivery Enhancement by Compounds of Natural Origin", Molecules., 2011, 16: 10507-10540.

[2] B. W. Barry, "Novel mechanisms and devices to enable successful transdermal drug delivery" Eur. J. Pharm Sci., 2001, 14: 101 - 114.

[3] R. H. Guy, Y. N. Kalia, M. B. Delgado-Charro, V. Merino, López A and Marro D, "Iontophoresis: electro repulsion and electro osmosis", J. Control. Rel., 2000, 64: 129- 132.

[4] R. Daniels, "Strategies for skin penetration enhancement" Skin Care Forum Issue., 2004, 37: 1-15.

[5] M. R. Prausnitz, "A practical assessment of transdermal drug delivery by skin electroporation" Adv. Drug Deliv Rev., 1999, 35: 61-76.

[6] B. E. Polat, D. Hart, R. Langer, D. Blankschtein, "Ultrasound-mediated transdermal drug delivery: mechanisms, scope, and emerging trends" J. Control. Release., 2011, 152: 330–348.

[7] Y. Mormito, M. Mutoh, H. Ueda, L. Fang, K. Hirayama, M. Atobe and D. Kobayashi, "Elucidation of the transport pathway in hairless rat skin enhanced by low frequency sonophoresis based on the solute water transport relationship and confocal microscopy," J. Control Release., 2005, 103: 587-597.

[8] S. Mitragotri, M. R. Prausnitz, R. Langer, "Current status and future potential of transdermal drug delivery," Nat Rev: Drug Discov., 2004, 3: 115–124.

[9] S. L. Tao and T. A. Desai, "Microfabricated drug delivery systems: from particles to pores," Advanced Drug Delivery Reviews., 2003, 55: 315-328.

[10] S. N. Murthy, "Magnetophoresis: an approach to enhance transdermal drug diffusion," Pharmazie., 1999, 54: 377-9.

[11] S. N. Murthy, A. Sen, Y. L. Zhao, and S. W. Hui, "pH influences the postpulse permeability state of skin after electroporation," Journal of Controlled Release., 2003, 93: 49-57.

[12] W. R. Lee, S. C. Shen, K. H. Wang, C. H. Hu and J. Y. Fang "The effect of Laser treatment on skin to enhance and control transdermal delivery of 5-flurouracil," J. Pharm. Sci., 2002, 91 (7): 1613-26.

[13] I. H. Blank, R. J. Scheuplein and D. J. Macfarlane "Mechanism of percutaneous absorption: The effect of temperature on the transport of non-electrolytes across the skin‖," J. Invest. Dermatol., 1967, 49: 582-589.

[14] F. Akomeah, T. Nazir, G. P. Martin and M. B. Brown, "Effect of heat on the percutaneous absorption and skin retention of 3 model penetrants," Eur. J. Pharm Sci., 2004, 21: 337-345.

[15] T. Ogiso, T. Hirota, I. Masahiro, T. Hino and T. Tadatoshi "Effect of temperature on percutaneous absorption of terodiline and relationship between penetration and fluidity of stratum corneum lipids," Int. J. Pharm., 1998, 176: 63-72.

[16] W. Hull "Heat enhanced transdermal drug delivery; a survey paper", J. Appl. Res. Clin. Exp. Ther., 2002, 2.

[17] R. J. Babu, N. Kanikkannan, L. Kikwai, C. Ortega, S. Andega, K. Ball, S. Yim and M. Singh, "The influence of various methods of cold storage on the permeation of melatonin and nimesulide," J. Control. Rel., 2003, 86: 49-57.

[18] A. Sintov, I. Krymbeck, D. Daniel, T. Hannan, Z. Sohn and G. Levin, "Radiofrequency microchanneling as a new way for electrically assisted transdermal delivery of hydrophilic drugs", J. Control. Rel., 2003, 89: 311-320.

[19] [19] M. Pellet, S. L. Raghavan, J. Hadgraft and A. F. Davis, "The application of supersaturated systems to percutaneous drug delivery", Transdermal drug delivery (Marcel Dekker), 2003, pp 305-326

[20] K. Swain, S. Pattnaik, S. C. Sahu, K. K. Patnaik and S. Mallick "Drug in adhesive type transdermal matrix systems of ondansetron hydrochloride: optimization of permeation pattern using response surface methodology," J. Drug Target., 2010, 18(2): 106-114.

[21] P. M. Elias, K. R. Feingold, J. Tsai, C. Thornfeldt and G. Menon, "Metabolic approach to transdermal drug delivery", Transdermal drug delivery (Marcel Dekker)., 2003, 285-304.

[22] S. S. Godavarthy, K. M. Yerramsetty, V. K. Rachakonda, B. J. Neely, S. V. Madihally, R. L. Robinson Jr, B. Godin and E. Touitou "Ethosomes: New prospects in transdermal delivery‖" Crit. Rev. Ther. Drug. Carrier., 2003, 20: 63-102.

[23] D. Abdullah, Q. N. Ping, and G. J. Liu, Yao Hsueh Hsueh Pao., 1996, 31, 214.

[24] M. Almirall, J. Montana, E. Escribano, R. Obach, and J. D. Berrozpe, Arzneimittelforschung., 1996, 46, 676.

[25] M. A. Yamane, A. C. Williams, and B. W. Barry, J. Pharm. Pharmacol., 1995, 47, 978.

[26] S. Porzio, G. Caselli, L. Pellegrini, V. Pallottini, M. Del Rosario, A. Coppola, L. Boltri, M. Gentile, G. Clavenna, and G. Melillo, Pharmacol. Res., 1998, 37, 41.

[27] A. Babar, P. J. Chickhale, and F. M. Plakogiannis, Pharm. Acta Helv., 1991, 66, 322.

[28] S. Kitagawa, H. Li, and S. Sato, Chem. Pharm. Bull., 1997, 45, 1354.

[29] C. A. Phillips and B. B. Michniak, J. Pharm. Sci., 1995, 84, 1427.

[30] D. D. Kim and Y. W. Chien, J. Pharm. Sci., 85, 214 (1996).

[31] [31] C. K. Lee, T. Uchida, K. Kitagawa, A. Yagi, N. S. Kim, and S. Goto, Biol. Pharm. Bull., 1993, 16, 1264.

[32] C. K. Lee, T. Uchida, E. Noguchi, N. S. Kim, and S. Goto, J. Pharm. Sci., 1993, 82, 1155.

[33] M. Okumura, Y. Nakamori, Y. Yoshida, H. Niwa, K. Sugibayashi, and Y. Morimoto, Drug Des. Deliv., 1990, 6, 137.

[34] M. Okumura, Y. Nakamori, K. Sugibayashi, and Y. Morimoto, Drug Des. Deliv., 1991, 7, 147 .

[35] S. C. Chi, E. S. Park, and H. Kim, Int. J. Pharm., 1995, 126, 267.