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REVIEW ARTICLE

Permeation enhancer strategies in transdermal drug delivery

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Abstract

Today, ~74% of drugs are taken orally and are not found to be as effective as desired. To improve such characteristics, transdermal drug delivery was brought to existence. This delivery system is capable of transporting the drug or macromolecules painlessly through skin into the blood circulation at fixed rate. Topical administration of therapeutic agents offers many advantages over conventional oral and invasive techniques of drug delivery. Several important advantages of transdermal drug delivery are prevention from hepatic first pass metabolism, enhancement of therapeutic efficiency and maintenance of steady plasma level of the drug. Human skin surface, as a site of drug application for both local and systemic effects, is the most eligible candidate available. New controlled transdermal drug delivery systems (TDDS) technologies (electrically-based, structure-based and velocity-based) have been developed and commercialized for the transdermal delivery of troublesome drugs. This review article covers most of the new active transport technologies involved in enhancing the transdermal permeation via effective drug delivery system.

Keywords

Iontophoresis, nano-carriers, permeation enhancement, sonophoresis, transdermal drug delivery

History

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Introduction

Transdermal delivery system is capable of transporting the drug through skin into the blood circulation at fixed rate. Transdermal route gives an alternative to oral and i.v. delivery. Benefits of local delivery are properly documented which includes targeted delivery, lower systemic exposure and lower toxicity than oral medications. This system is also helpfull in the treatment of hair loss, neuropathic pain, acne, genital herpes, migraine, headaches and sexual dysfunction (Singh et al., 2014a). It comprises list of advantages over conventional routes such as:

- Transdermal delivery avoids the stomach environment where the drug can be degraded (Singh et al., 2012b).
- Transdermal delivery avoids the first pass effect where active drug molecules can be converted to inactive molecules or even to molecules responsible for side effects (Singh et al., 2012a).
- Provides steady plasma levels.
- Easy to use and non-invasive.
- Drug input can be stopped at any point after removal of the patch from the site (Singh et al., 2014c).
- Increases compliance and reduces medical costs.
- Improves bioavailability.
- Best route for pediatrics patients.
- Suitable route for unconsious or vomiting patient.
- Lesser chances of overdose and easy detection of drug (Durand et al., 2012).

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Human skin: penetration barrier

Human skin covers the largest part of the body. The primary function of the skin is to maintain the body hydration (Fukushima et al., 2011). Figure 1 demonstrates cross-sectional area of skin. Skin are comprised of three layers.

Stratum corneum

The exposed layer of the skin (also termed as horny layer) which is approxmateily 10 mm thick. It has barrier property due to presence of 79–90% of protein and 5–15% of lipids. The multilayered epidermis varies in thickness which mainly depends upon cell thickness and layers of epidermis. Table 1 represents the reginoal variations (thickness, water permeability and diffusivity of water) in drug permeability through epidermis (Patel & Baria, 2011).

Dermis

Thickness of this layer is ~3–5 mm. It mainly consist of connective tissues, mandatory in regulation of body temperature, oxygen, nutrients to the skin and removing toxic products (Singh et al., 2014b).

Hypodermis

It holds the fat tissues and acts as a support memberane for both epidermial and dermal layer of skin. It has its own importance in transdermal drug delivery. Drug shall penetrate through all three layers to reach systemic circulation (Sun et al., 2014).

Figure 1. Cross-sectional area of skin.

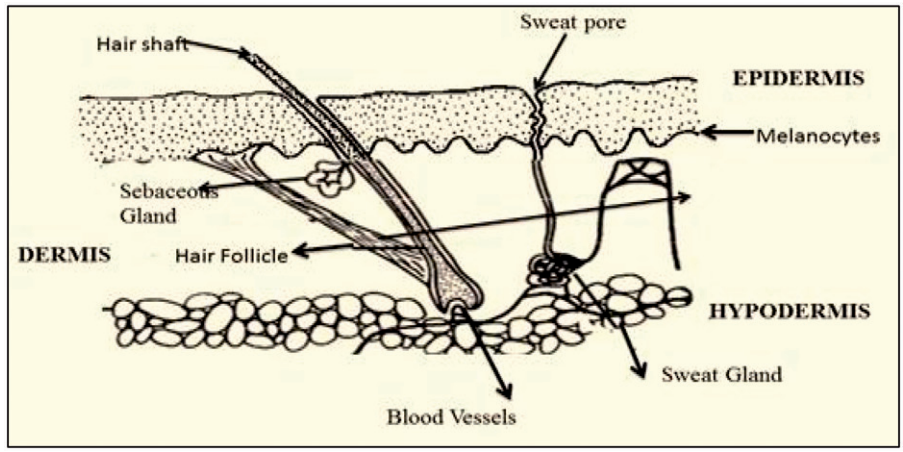

Table 1. Regional variations in drug permeability of stratum corneum.

Skin region	Thickness (μm)	Permeation rate (mg/cm^2/h)	Permeability coefficient	Diffusivity (cm^2/s × 10^{10})
Abdomen	15.00	0.34	0.02266	6.00
Volar forearm	16.00	0.31	0.01937	5.9
Back	10.5	0.29	0.027619	3.5
Forehead	13.00	0.85	0.065384	12.9
Back of hand	49.00	0.56	0.011428	32.3
Palm	400.00	1.14	0.002850	535.00

Drug penetration pathway

Drug can be penetrated by three pathways such as transcellular route, paracellular lipid route and transappendgeal route (Figure 2).

- *Transcellular Route*: Moeity passes through both keratinocytes and lipids (straight path to the dermis) (Ghaffarian & Muro, 2013).
- *Paracellular Route*: The most common penetration pathway of drug molecules. In this pathway, drug remains in lipid moeity and stay around keratin (easy for lipid soluble drug rather than proteins) (Parnami et al., 2013).
- *Transappendgeal Route*: It makes continues channel for drug permeation but it hindered easily due to presence of hair follicles and sweat ducts (Sharma et al., 2011).

Factors affecting transdermal drug delivery

Physiochemical properties of active moiety (Dhote et al., 2012; Park et al., 2012)

Partition coefficient

Drug possess both water and lipid solubility. Ideal partition coefficient for intermediate trasdermal delivery is log K 1–3. For highly lipophillic drug (log $k > 3$), intracellular route is favourable, whereas for hydrophillic drugs (log $k < 1$), it is permeated via transcellular route.

Molecular size

Molecular size of the drug is inversaly proportional to transdermal flux. The ideal molecular size of drug molecule for transdermal delivery is $\leq$400.

Solubility/melting point

Most organic solutes have high melting point and low solubility at normal temperature and pressure. Lipophillic drug permeates faster than hydrophillic substances, but it should also have aqueous solubility as needed in most of topical formulations.

Ionization

Unionized drug permeates the skin as according to pH-Partition hypothesis.

Diffusion coefficient

Penetration of drug depends on diffusion coefficient of drug. At a constant temperature, the diffusion coefficient of drug mainly depends on properties of drug, diffusion medium and their interaction.

Physiochemical properties of the drug delivery system (Rehman & Zulfakar, 2014; Schoellhammer et al., 2014)

Release characteristics

Drug release mechanism mainly depends on drug molecules which are dissolved or suspended in the delivery system and on interfacial partition coefficient or pH of the drug from delivery system to the skin tissue. If the drug is easily released from the delivery system, the rate of transdermal permeation will be higher.

Composition of drug delivery system

Composition may not affect release properties but may affect its permeability functionality. For example, methyl salicylate is more lippophilic than parent acid, i.e. salicylic acid, and its percutaneous absorption is high when applied to skin in a lipoidal vehicle.

Enhancement of transdermal permeation

Majority of drugs will not permeate into skin for theraputic use. Some enhancers are used for syergistic action without showings its properties (e.g. dimethyl sulphoxide, acetone, propylene glycol and tetradihydrofuryl alcohol).

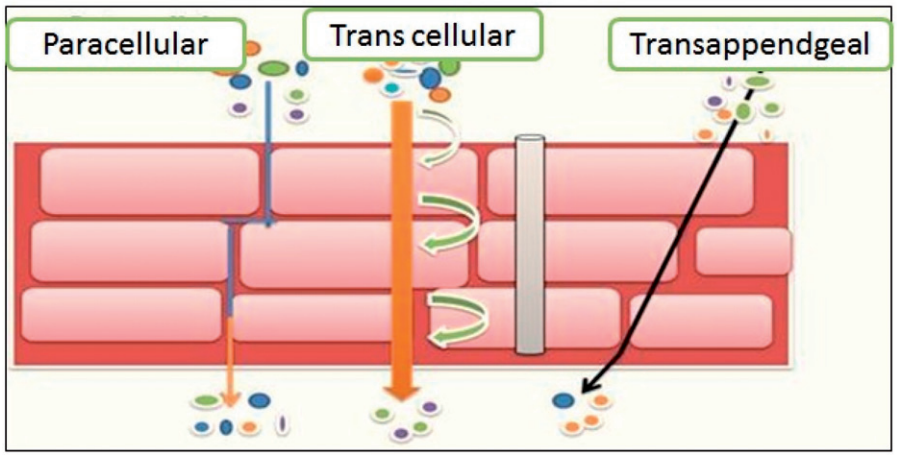

Figure 2. Drug permeation pathway through skin.

Physiological properties (Jones & Moss, 2010; Subedi et al., 2010)

Skin barrier properties in the neonate and young infant

The skin surface of the newborn is slightly hydrophobic, relatively dry and rough when compared to that of older infants. Stratum corneum hydration stabilizes by the age of 3 months.

Skin barrier properties in aged skin

There are some changes in the physiology of aged skin (>65 years). The moisture content of human skin decreases with age. There is a destruction of the epidermal junction and consequently, the area available for transmission into the dermis is diminished.

Race

Racial differences between black and white skins have shown some anatomical and physiological functions of the skin. In black skin, there is increased intracellular permeation due to higher lipid content and higher electrical skin resistance levels when compared to whites, but this difference is not detected in stripped skin.

Skin temperature

The human body maintains a temperature of ~32–37 °C across the skin. Hence, increase in temperature leads to increase in diffusion through the tissue (Vinod et al., 2010).

Various issues with transdermal and topical delivery system

(1) Not very helpful for gedriatric patients because skin undergoes various deformations and alterations (lipids and protein composition changes) (Kaur et al., 2014c).
(2) Irritant dermatitis is the most common reaction reported with many transdermal delivery systems. It is an inflammatory reaction which is non-allergic and their skin may be more fragile or react more easily (Brown & Langer, 1988; Fowler et al., 2009).
(3) Allergic contact dermitis with intense erythema, intense itching, redness and blistering are common. The reaction tends to magnify for a few days after the transdermal delivery system is removed (Kaur et al., 2014b).
(4) Causes allergic contact urticaria (ACU) is type I hypersensitivity reaction, with IgE-mediated inflammatory response to a specific allergen (Mackay et al., 2001).
(5) Products which contain vasodilators (nitroglycerin and nicotine) or pressure-sensitive adhesives can cause a transient reactive hyperemia (Murphy & Carmichael, 2000).
(6) Transdermal delivery system that has a metallic component (usually aluminum) in their waterproof layer can cause burns if they absorb heat. Products are not always labeled with a warning if they contain metals (Elmoslemany et al., 2012).

Strategies applied for permeation enhancement

Drawback of transdermal delivery is permeation of active moeity through skin. So, various studies are done for enhancing its permeability percutaneously. Figure 3 depicts various strategies for increament of pentration. They act by three mechanisms:

(1) By altering physicochemical properties of stratum corneum.
(2) By changing hydrating property of stratum corneum.
(3) By altering structure of lipids and protein in intercellular channel via carrier mechanism (Csizmazia et al., 2012).

Drug/vehicle interaction

Drug and prodrug selection

Active ingredient to be used should be judiciously chosen on the bases of pharmacological or physiochemical properties.

Ideal properties for drug selection are:

- Less than 600 Da is prefered when diffusion coefficient is high.
- Good solubility in oil and water.
- High and adequate partition coefficient (1–3).
- Should carry melting point <200°F.
- It should not metabolize in skin (Kataria et al., 2014; Kaur et al., 2014a).

Ion-pair

Though active moeity, which can penetrate into skin, is a charged molecule, it cannot be permeate. However, lipophilic ion pair technique can enhance epidermal penetration.

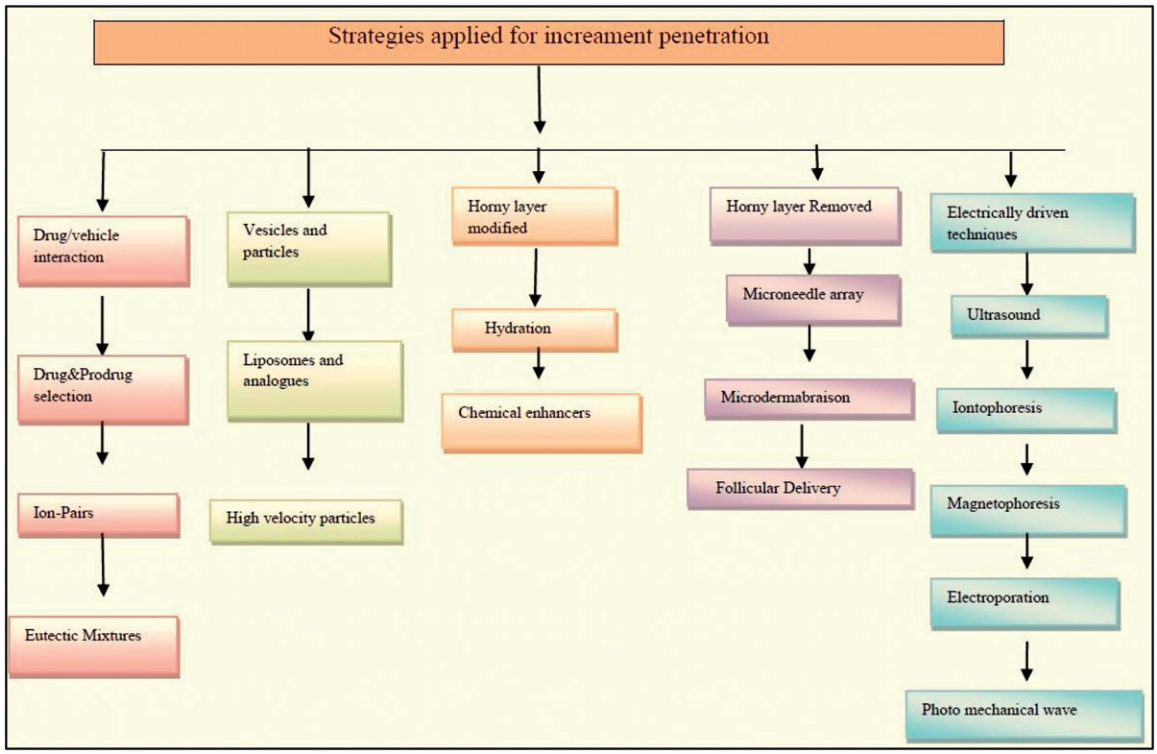

Figure 3. Advance strategies to overcome problems related to transdermal delivery.

In this technique, oppositely charged species forms pair and neutralize the charge as well as dissociates in viable aqueous epiderms and realesing parent molecule (Goyal et al., 2013b). The coacervate permeates in skin as it diffuses or dissociates and behaves like ion pair (Goyal et al., 2013a). Valenta et al. determine the significance of ion pairing on the permeation of lignocaine. Diffusion studies were performed through polydimethylsiloxane (PDMS) at different pH values 4.0, 6.0, 7.0 and 8.0. The steady state lignocaine flux was increased up to 2.45-fold using different counter ions. The highest flux was measured from lignocaine morpholinopropane sulfonate (L-mps) (Valenta et al., 2000). Riserdronate is an inhibitor of osteoclastic activity used for treating various disorders of bones. It is highly ionized and very acidic which leads its low permeating properties into skin. Found out ion-paired solution with L-arginine which were tested *in vitro* on hairless mouse. The result showed that flux was increased, i.e. $14.13 \pm 5.49\,\mu g/cm^2$ to 36 times ($475.18 \pm 94.19\,g/cm^2$ and $511.21 \pm 106.52\,g/cm^2$) (Nam et al., 2011).

Eutectic mixtures

Solubility is a factor which is mostly affected by melting point of a substance (directly affects skin permeation). The lower the melting point, more will be solubility in lipids of skin (Garg & Goyal, 2014c). For lowering the higher melting point, we make eutectic mixtures (a mixture of two components which at a certain ratio due to which crystalline phase is inhibited) so that melting point of two components is less than the single component (Fiala et al., 2010). For example, ibuprofen with terpenes, menthol with methyl nicotine, propranolol with fatty acids and lignocaine with menthol. Analgesics such as NSAIDs have gastrointestinal side effects and topical dosage forms of these drugs are mainly preferred, especially for local pains. Meloxicam is one of NSAIDs with no topical form in the market. Mohammadi-Samani et al. (2014) aimed to design a formulation of meloxicam for transdermal delivery using thymol as the penetration enhancer. *In vitro* permeation studies showed that 5.5 ratio (Melocxicam:Thymol) in guinea pig have maximum flux, i.e. $22.06\,\mu g/cm^2$ (Mohammadi-Samani et al., 2014).

Horny layer modification

Hydration

Water is the best way for permeating both hydrophillic and hydrophobic drugs. In normal conditions, 10–20% concentration is present in stratum corneum. Hydration of epidermis is an important aspect for permeation enhancement. In this technique, water-soaked skin can absorb a generous amount of water in a short span of time. Natural Mosturizing Factor (NMF) acts as mediator for hygroscopic property of corneum. It mainly consist of free amino acids and their salts. Skin hydration causes swelling of kertins and effecting lipid packing as well as interupting polar and non-polar routes (Haftek et al., 1998). Table 2 explains hydration affects on skin permeability via various pharmaceutical systems.

Chemical enhancer

Chemical enhancers help in permeation across the skin by disruption of the highly ordered structure of stratum corenum lipid, interaction with intercellular protein or improve

Table 2. Effects of hydration on skin permeability.

Delivery system	Constituents	Effects on hydration	Skin permeation
Occlusive dressing	Unperforated plastic films	Full hydration	Marked increase
Occlusive patch	Imperforated patches	Full hydration	Marked increase
Lipophilic material	Paraffins, oils, fats, waxes, fatty acids and alcohol, esters and silicones	May or may not produce full hydration	Marked increase
Absorption base	Anhydrous lipid material	Marked hydration	Marked increase
Emulsifying base	Anhydrous lipid material	Marked hydration	Marked increase
Water–oil emulsion	Oily creams	Raised hydration	Increase
Humectant	Glycerols, glycols	Slight hydration	Slight property
Powder	Clays, organics, inorganics	Decreased hydration	Penetration enhancer
Oil–water emulsion	Aqueous creams	Slight hydration	Very little effect

partition of the drug into stratum corneum (Garg et al., 2013). Chemical enhancers should contain the following properties:

- It should be non-toxic and non-allergen.
- It should have rapid working activity and the duration should be predictable (Garg et al., 2012d).
- It should be unidirectional.
- Its compatibility with both excipients and drugs.
- Its properties according to drugs and cosmetic act (Erdal et al., 2014).

Classification of percutaneous chemical enhancers

The classification of percutaneous enhancers is frequently based on the chemical class to which the compounds belong. Table 3 shows the principal classes of percutaneous enhancers.

Table 3. Enlisting various chemical enhancer on the bases of their structure.

Chemical class	Compounds
Water	Water
Hydrocarbons	Alkanes, alkenes, squalene, mineral oil, halogens
Alcohols	Glycerols, glycols, polyglycols, ethanol, caprylic alcohol
Acids	Oleic acid, Undecanoic acid and other fatty acids
Amines	Primary, secondary and tertiary, cyclic and acyclic amines
Amides	Pyrrolidone(*N*-methyl-2-pyrrolidone, 2-pyrrolidon)azones (Azone® (1-dodecylazacycloheptan-2-one))urea
Esters	Isopropyl myristate
Surfactants (anionic, cationic, non-ionic, Zwitterionic)	Sodium lauryl sulfate, cetyltrimethyl ammonium bromide, sorbitan monolaurate, polysorbate 80, dodecyl dimethyl ammoniopropane sulfate
Terpenes, terpenoids and essential oils	Menthol, limonene
Sulfoxides	Dimethyl sulfoxide, dodecyl methyl sulfoxide
Lipids	Phospholipids

Horny layer removed

Microneedle array

Microneedles are devices which act as both hypodermic needles and transdermal patch. It consists of drug pool and some protrusion termed as microneedles which helps in drug permeation across without reaching nerve (Figure 4). These needles are 200–750 microns in length and are composed of groups called arrays which contains 150–650 microneedles/cm^2 and have diameter of tip 25 μm interfacial area of 490 μm^2 with an insertion force required is 0.058 N. Materials which makes these arrays are silicon, metal, sugar and plastics (Duan et al., 2011). These can be of four kinds: (i) Poke with patch approach (excruciating into epidermal layer and applying patch locally), (ii) Coat and poke approach (needles incorporated with drug, release of pharmacological active moeity takes place by dissolution), (iii) Biodegradable Microneedle (insertion of drug incorporated polymeric microneedle which is biodegradable) and (iv) Hollow Microneedle (puncturing epidermal surface with needles with a hollow bore) (Garg et al., 2011d). Various formulation under clinical trials. Good technique for large molecular weight drugs, e.g. insulin, hormones, calcitonin and various peptides and proteins (Donnelly et al., 2014). Table 4 shows various microneedle projects at different stages of clinical trials.

Recent marketed product of ALZA Corporation named Macro flux® estimated to be ~50–200 μm and therefore are not believed to reach the nerve endings. Kim et al. (2012) enhanced hydrophillic peptides such as oxytocin, tetrapeptide-3, hexapeptide with pretreatment with microneedle array within porcine ear skin and achieved a positive correlation with weight of peptides (Kim et al., 2012).

Stratum corneum removed

Microdermabrasion is introduced as a method to increase skin permeability by selectively removing the stratum corneum. The depth of slash depends on patient's requirement. This technique is boon to large molecular weight drugs like peptides, insulin and vaccines. In this method, complete removal of epidermis is not employed. Skountzou et al. observed transcutaneous immunization using topical delivery of influenza vaccine. The outer skin barrier can be overcome through the use of mild chemical and/or physical treatments, including ethanol–water hydration and stripping, which allows large vaccine molecules or even particulate antigens to gain access to the skin's immune cells (Skountzou & Kang, 2009). Microdermabrasion can be achieved via three promising ways.

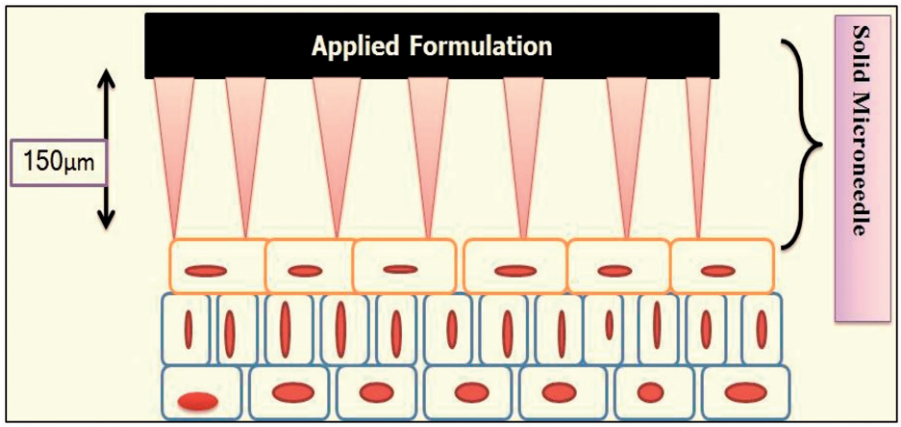

Figure 4. Enhancement of transdermal permeation by microneedle array.

Table 4. Microneedles projects under clinical trials.

Study	Target	Phase	Sponsor	Updated
Lidocaine w/Micronjet®	Local analgesia	Pilot	NanoPass Tech.	11/07
Safety/PK/PD of insulin w/Micron Jet®[44]	Diabetes	Pilot	NanoPass Tech.	4/08
Insulin delivery w/microneedle	Type I diabetes	Phase II/III	Emory Univ.	2/09
Microarray delivery of lidocaine	Topical anesthesia	Phase II/III	Univ. of OK	6/10

Microdermaabrasion with histological imaging

Basically, this technique is applied for beauty treatment for removing scars and wrinkles. Aluminium oxide crystals (pressure 30–35 kPa), aluminium oxide diamond, magnesium oxide and sodium bicarbonate are also used for this purpose (Garg & Goyal, 2014a).

Dye penetration

Dyes should be approved by FDA and Cosmetic act. These techniques are maily used for tatoo removal or permanent make up (Garg et al., 2012c).

Skin electrical resistance

An average specific resistance ($1750 \pm 1340\,k\Omega\,cm^2$) is required for stratum corneum removal (Garg et al., 2014).

Follicular delivery

Therapeutically, active drug can be penetrated through sweat glands and hair follicles (rich invascularization) (Terminal Hair Follicles $172 \pm 70\,\mu m$, Sebaceous Follicles $86 \pm 37\,\mu m$).

These hydrophillic as well high molecular weight moieties can act as storage for min. upto 10 days. This technique is best suited for topical preparations (Garg et al., 2011c).

Electrically driven technique

Ultrasound

It is also termed as phonophoresis or sonphoresis. In this enhancement technique, permeation is increased via ultrasonic waves which means frequency is >20 kHz which is shown in Figure 5. Mechanism involves either of the two ways: (a) application of sound waves to the skin increases to fluidity of lipids and increases permeation via transcellular pathway or (b) formation of bubbles which generates pores which even allows large molecular weight drugs such as protein or vaccines. Trainers prefer this method to permeate dexamethasone, ketoprofn or lidocaine in patients. But this techinique has some limitations, i.e. formation of attenuation which is due to the fact that sound waves transforms to heat energy (Tiwari et al., 2004). The additional advantages, limitations and applications that the ultrasound technique comprises are summarized in Tables 5 and 6, respectively.

Iontophoresis

It is defined as permeation of ionized drug through electrical impulses of 0.5 mA/cm by either galvanic or voltaic cell (Figure 6). It contains cathode and anode which attracts positively charged ion and negatively charged ions, respectively (Garg & Goyal, 2012). Its mechanism strictly follows Faraday's law.

$D = IT/(\mathrm{IZI})F$, where D is the drug to be permeated, I is the current (amperes), IZI is the valance and F is the Faraday's constant (coloumb/Mol). According to this equation, drug drawn into skin is directly proportional to current applied. pH of skin plays an important role, higher the pH of the skin more will be the permeability in the skin. Iontophoresis shows the action in either way such as electromagnation, in which charged ions is attracted to oppositively charged electrode or electroosmosis in which non-ionic substance permeates with solvent (Dhote et al., 2012). Hashim et al. (2010) studied topical application of nuclear factor-kappa B (NF-kappa B) decoy in the treatment of inflammation and atopic dermatitis. The results suggest that iontophoresis is a useful and promising enhancement technique for transdermal delivery of NF-kappa B decoy ODN (Hashim et al., 2010). Gomez et al. (2012) studied topical delivery of calcium and phosphate for treatment of osteoporesis. The results showed an increase in bone density by restoration of calcium and phosphate in bone (Gomez et al., 2012). Table 7 discusses

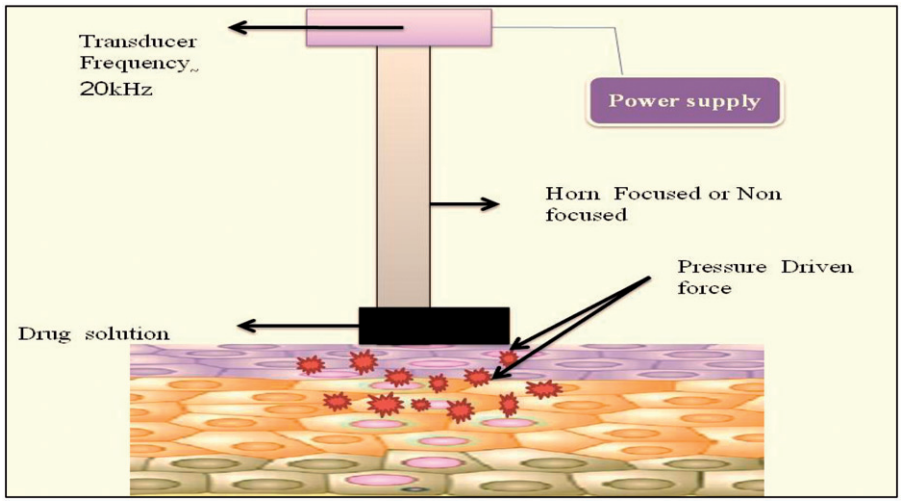

Figure 5. Enhancement of transdermal permeation by ultrasound technique.

Table 5. Advantages and limitations of ultrasound techniques.

Advantage	Limitations
Enhanced drug penetration	Time-consuming to administer
Controlled release	Cause tingling
Patient satisfaction	Cause irritation
Less risk of systemic absorption than injection	Cause burning

various advantages and limitations of iontophoresis technique.

Types of iontoporesis

Direct iontoporesis. Anions are permeated through passive diffusion.

Reverse iontoporesis. It allows the movement of neutral and positive ions into cathode and negative ions into anode. Future expectation for delivery of large molecular weight drugs like calcitonin, inulin, gonadotropin releasing hormone, parathyroid hormone,vassopresin and insulin can be actively deliverd by this mechanism (Gagandeep et al., 2014). At present, apomorphine is used for treatment of idiopathic Parkinson's disease in many volunteers and it has good future in diagnosis of cystic fibrosis (Garg et al., 2011b).

Magnetophoresis

This enhancement technique involves applying magnetic field around the solute *that* penetrates into the skin. For example, benzoic acid is a diamagnetic substance and when the magnetic field is applied around, it increases diffusion properties, as shown in Figure 7. The major limitation associated with this technique is that, it might change properties of stratum corneum (Garg, 2014).

Electroporation

This application involves short electrical pulses of DC voltage >100 V for milliseconds (Figure 8). This technique works in either of the two ways: first is pore formation in lipid bilayers, corneocytes but small-charged molecules cannot pass via this route and the second is applying high voltage which automatically creates aqueous pores through epidermis which are helpful in permeation across five to six lipid membranes (Arora et al., 2012). Eriksson et al. (2013) studied that DNA vaccine (coding for prostate specific antigen to treating prostate cancer) can be given transdermally with the help of electroporation technique. Patients with good biochemical relapse of prostate cancer were observed (Eriksson et al., 2013). It has positive applications in delivery of proteins, oligonucleotides, small molecules, heparin, insulin, dextran and vitamin C. Electroporation are of two types.

Reversible

Electric pulses cause short-term increment in permeation enhancement and cell survives. This approach has its application in biotechnology and medicine.

Irreversible

Electric pulses lead membrane permeation which leads to cell death or necrosis or apoptotic. This approach has its application in food industry and sterlization.

Photomechanical wave

It is also termed as laser-generated stress pressure wave, which is generated by incision of the targeted substance polystyrene. It has no specific mechanism of action, but it changes the lacnuar system in the epidermis as shown in Figure 9. This technique is capable in delivering of macromolecules (40 000 Da). It is used in dermatalogical techniques such as skin rejuvenation and acne scar's healing (Lee et al., 1999).

High-velocity particles

Powderject device

It consist of propulsion of solid drug into skin by gas (helium) as medium with a speed of 600–900 m/s (Figure 10). This technique is painless and non-invasive. This system ruptures the epidermal layer which is reversible in nature. Postive outcomes of this technique are delivery of testosterone, lidocaine hydrochloride and macromolecules such as calcitonin and insulin (Degano et al., 1999).

Table 6. Research application of ultrasound techniques.

Research	Outcomes	References
Anticancer drugs		
Application of a method using ULTS and nano/micro bubbles to cancer gene therapy using prodrug activation therapy	Dramatic reductions of the tumor size by a factor of four	Hou et al. (2009)
Investigation of competitive transport across skin of 5-fluorouracil into coupling gel under the influence of ULTS, heat-alone and Azone® enhancement	Ultra sonication produced a decrease in percutaneous drug penetration. This effect was due to the diffusive loss of the hydrophilic substance 5-fluorouracil from the skin surface	Cao et al. (2011)
Mechanical exfoliation using micro dermabrasion has been used with electrically assisted percutaneous delivery of macromolecules (Hyaluronic acid, retinol, peptide containing complex), relies on ultrasonic waves producing alterations within the stratum corneum that result in increased absorption	Propelled microdermabrasion followed by ultrasonic phono phoretic application of topical products represents a novel dermal delivery approach to photo rejuvenation	Dudelzak et al. (2008)
Insulin		
To determine if the 3×1 rectangular cymbal array perform significantly better than the 3×3 circular array for glucose reduction in hyperglycemic rabbits	Using the rectangular cymbal array, the glucose decreased faster and to a level of -200.8 ± 5.9 mg/dl after 90 min	Luis et al. (2007)
To demonstrate ultrasonic transdermal delivery of insulin *in vivo* using rabbits with a novel, low profile two-by-two ULTS array.	For the ULTS-insulin group, the glucose level was found to decrease to -132.6 ± 35.7 mg/dL from the initial baseline in 60 min	Barker et al. (2013)
Hormones		
Effect of permeation enhancers and application of low frequency (LUS) and high-frequency ultrasound (HUS) on testosterone (TS) transdermal permeation after application of testosterone solid lipid microparticles (SLM).	Skin exposure to HUS or LUS before application of 1% dodecyl amine for 30 min had no superior enhancement effect over application of either LUS or HUS alone. Application of drug loaded SLM offered skin protection against the irritation effect produced by TS and 1% DA	El-Kamel et al. (2008)

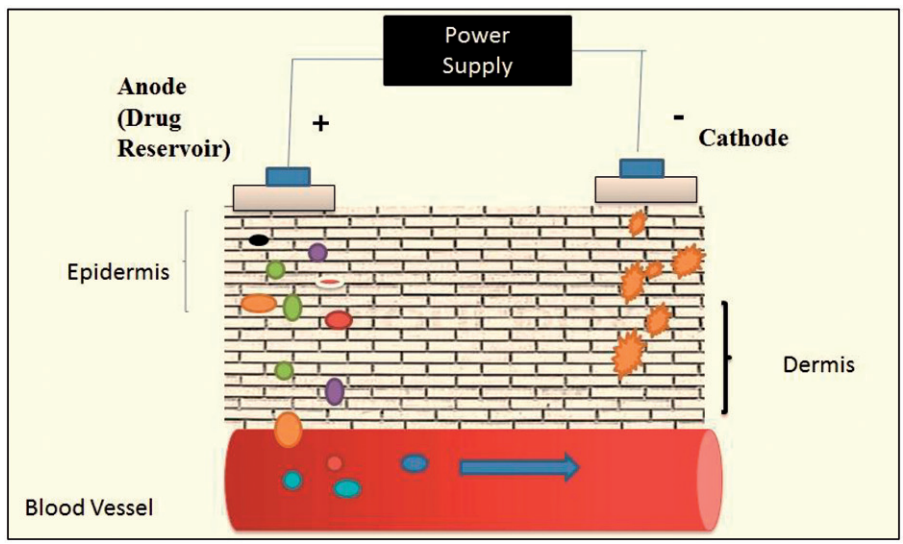

Figure 6. Enhancement of transdermal permeation by iontophoresis technique.

Table 7. Advantage and limitations of iontoporesis technique.

Advantage	Limitations
Improved polarised drug permeation	Cannot permeate drug of molecular weight >7000 Da
Improved transport for proteins	Time consuming process
Donot produce skin erythmea	Irreversible damage to skin properties
Delivery of drug depends on electric current nor skin properties	Bad functioning of microprocessor
Improved transport for oleigonucleotide	Limitation to use current in human skin

Needle-free injections

This method consist of non-invasive technique which is boon over conventional dosage form. Some of its injectors are as follows:

Intrajet: It uses nitrogen propelled gas. Patient breaks up the tip and presurized gas forces the liquid drug into generated small pores.

Implajet: It pushes a fine needle into the skin with opens channels and drug permeates immediatly.

Jet-syringe: This is capable of delivering 0.5 ml dose into the skin. It is best for short therapies.

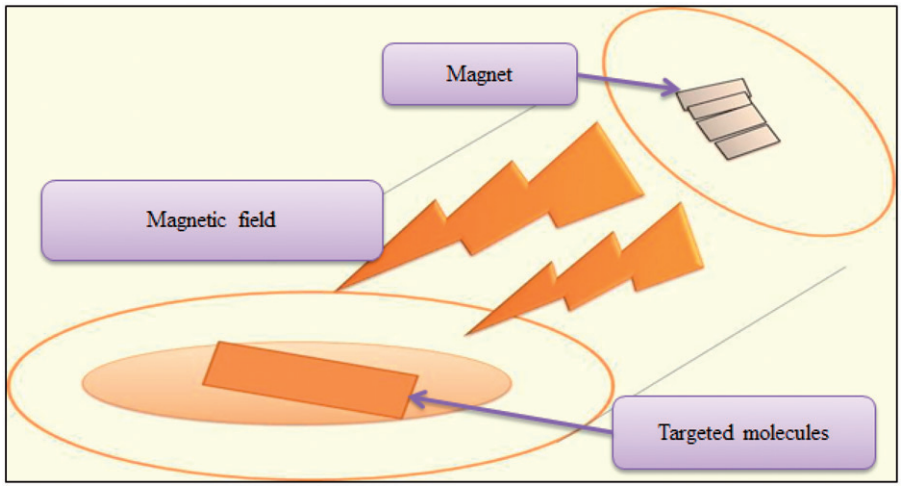

Figure 7. Enhancement of transdermal permeation by magnetophoresis technique.

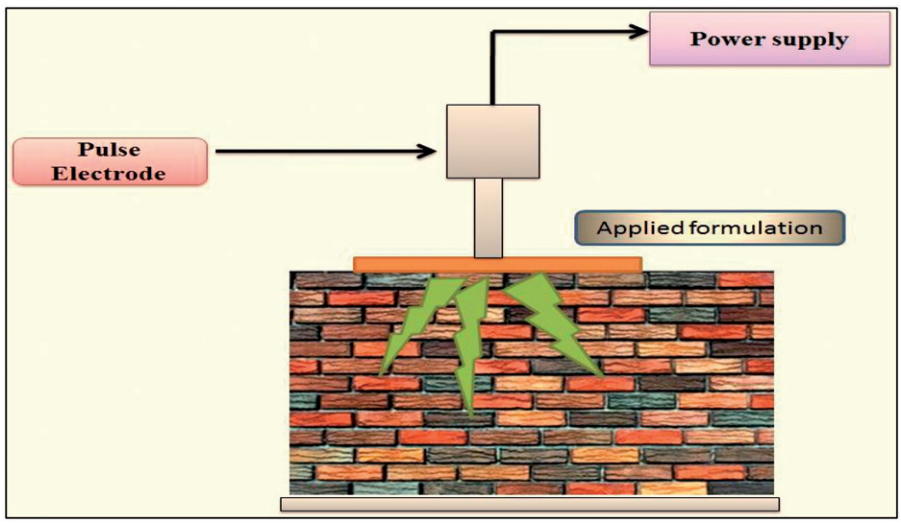

Figure 8. Enhancement of transdermal permeation by electroporation technique.

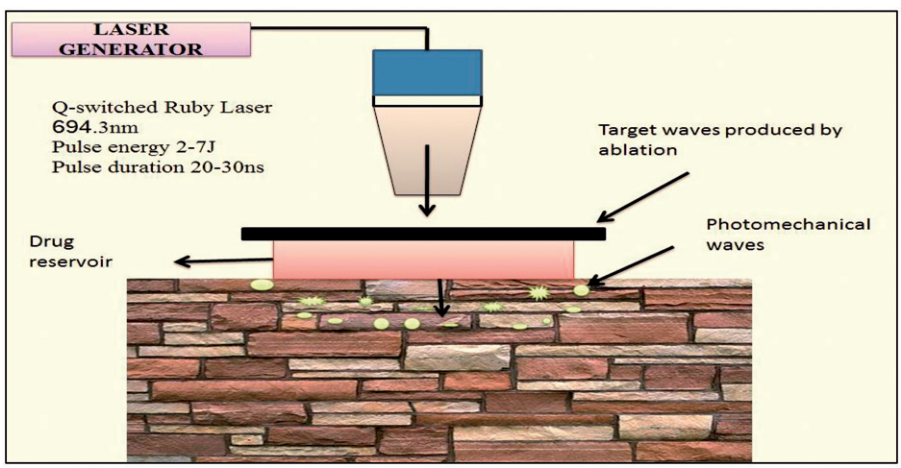

Figure 9. Enhancement of transdermal permeation by photochemical wave devices.

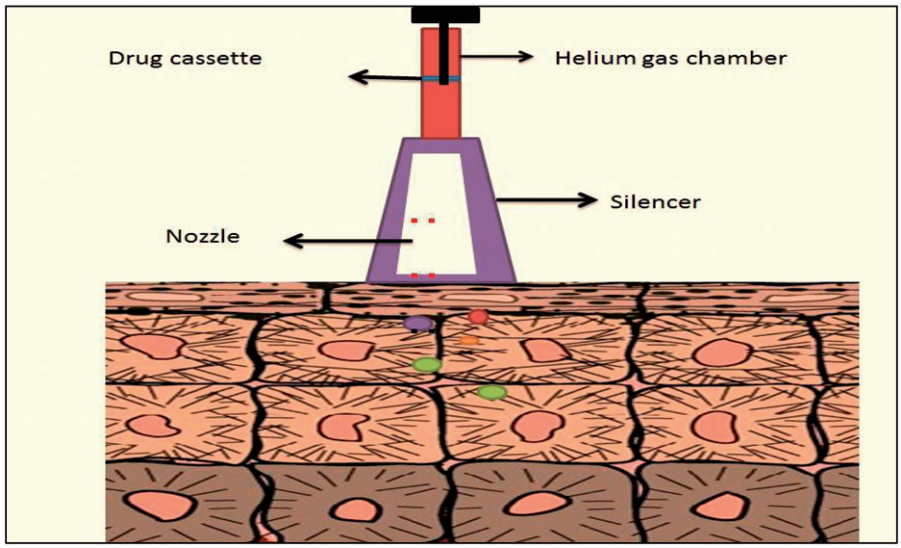

Figure 10. Powderject devices: a needle-free tool for transdermal drug delivery.

Table 8. Proposed mechanism of drug absorption through different drug delivery carriers.

Formulation	Drug	Proposed mechanism	Conclusion	Reference
Liposomes and niosomes	Enoxacin	Permeation enhancer effect and direct vesicle fusion with stratum corneum	Ability to modulate drug delivery without toxicity and makes the two vesicles useful to formulate topical route.	Fang et al. (2001)
Niosomes	Gallidermin	No absorption due to large molecular structure of Gallidermin as well as the large niosomal structure	Gallidermin loaded in anionic niosomes and incorporated in gel is the superior topical anti-bacterial formulation because of high accumulation in the skin with no risk of systemic effect.	Manosroi et al. (2010)
Bola-niosomes	5-fluorouracil	Bola surfactant contributes flexibility and deformability of the structure which enables them to pass through human skin similarly to ethosomes and transferosomes	Bola-niosomes were able to promote the intracellular delivery thus improving the anti-cancer activity of the entrapped 5-fluorouracil	Bei et al. (2010)
Cationic transferosomes	Topical genetic vaccine against hepatitis B	Inducing strong humoral and cellular immune response	Cationic transferosomes were capable of inducing strong humoral and cellular immune response after topical administration	Li et al. (2014)
Ethosomes	Lamivudine	Lipid perturbation and increasing the intercellular lipid lamellae space of stratum corneum	Lipid perturbation along with elasticity of ethosomes vesicle seems to be the main contributor for improved skin permeation	Jain et al. (2007)
Invasomes	Temoporfin	Synergistic effect of liposomes, terpenes and ethanol	Invasomes containing 1% of terpenes mixture present an effective drug carrier system for delivering the highly hydrophobic drug Temoporfin into the stratum corneum and deeper layers of skin.	
Penetration enhancer-containing vesicles	Minoxidil	Intact vesicle penetration by entering the stratum corneum where they form a depot from which the drug is slowly released	Penetration enhancer-containing vesicles can be a potential innovative carriers for improving topical delivery of minoxidil	
Deformable liposomes	Methotrexate	By transcutaneous hydration force	Deformable liposomes improve *in vitro* skin delivery compared to either aqueous solution or normal liposomes.	Romero & Morilla (2013)

(*continued*)

Table 8. Continued

Formulation	Drug	Proposed mechanism	Conclusion	Reference
Ethosomes	Melatonin	Increase in thermodynamic activity due to evaporation of ethanol, increases penetration of drug molecule due to reduction in barrier property of stratum corneum by ethanol.	Ethosomes bearing melatonin offered a suitable approach for transdermal delivery when compared to liposomes and hydroethanolic solution.	Dubey et al. (2007)
Liposomes	Curcumin	Curcumin/curcuminoids were encapsulated in phosphatidylcholine vesicles with high yields for targeting transmucosal vaginal.	liposomes bearing pure curcumin were promising delivery systems.	Basnet et al. (2012)
Biphasic lipid vesicle	Interferon-α	Bipahsic lipid vesicles incorporate Interferon-α,which applied topically	Biphasic vesicles delivered clinically significant levels of IFN α across intact human skin and elicited marked therapeutic effect in patients	Foldvari et al. (2011)
Nanoparticle	Tadalafil, sialorphin	Nanoparticles encapsulating the erectogenic agents were applied as a gel to the glans and penile shaft of anesthetized Sprague–Dawley rats.	Nanoparticles encapsulating three different erectogenic agents resulted in increased erectile function when applied to the penis of a rat model of ED. Nanoparticles represent a potential novel route for topical delivery of erectogenic agents which could improve the safety profile for existing orally administered drugs	Han et al. (2010)
Biodegradable nanoparticles	Targeted delivery of PSC-RANTES for HIV-1	PSC-RANTES PLGA nanoparticles formulated via a double emulsion process	Studies indicates PSC-RANTES can readily be encapsulated into a PLGA nanoparticle drug delivery system, retain its anti-HIV-1 activity, and deliver PSC-RANTES to the target tissue.	Ham et al. (2009)
Elastic liposome	Interleukin (IL)-13	IL-13 antisense oligonucleotide (ASO) was designed and formulated with cationic elastic liposome (cEL)	IL-13 ASO/cEL-treated AD mice showed reduced infiltration of inflammatory cells into the epidermal and dermal areas, with concomitant reduction of skin thickness.	Kim et al. (2009)
Microemulsion	CyclosporinA	Micro-organogel comprising cyclosporin A was applied on rat skin	The deposition of the drug into skin and subcutaneous fat was, respectively, almost 55- and 3-fold higher than the concentrations compared with oral administration.	Liu et al. (2007)
Cationic transferosomes	Hepatitis B surface antigen	Cationic transferosomes composed of cationic lipid DOTMA and sodium deoxycholate as constitutive lipids were prepared, DNA encoding hepatitis B surface antigen (HBsAg) was loaded in the cationic transferosomes using charge neutralization method	It was also observed that topical application of DNA-loaded cationic transferosomes elicited a comparable serum antibody titer and endogenous cytokines levels as produced after intramuscular recombinant HBsAg administration	Mahor et al. (2007)
Hybrid nanoparticles	Capsaicin (Cap) and anti-TNFα siRNA (siTNFα)	Encapsulation of antinociception in cyclic cationic head lipid-polymer hybrid nanocarriers (CyLiPns) against chronic skin inflammatory diseases	Novel cationic lipid-polymer hybrid nanoparticles can efficiently carry siTNFα and Cap into deeper dermal milieu and Cap with a combination of siTNFα shows synergism in treating skin inflammation.	Desai et al. (2013)

(*continued*)

Table 8. Continued

Formulation	Drug	Proposed mechanism	Conclusion	Reference
SPACE ethosome	Hyaluronic acid	The peptide was conjugated to phospholipids and used to prepare an ethosomal carrier system (~110 nm diameter), encapsulating HA(200–325 kDa)	Concentrations of HA in skin were ~1000-fold higher than those in blood; confirming the localized nature of HA delivery into skin. The SPACE-ethosomal delivery system provides a formulation for topical delivery of macromolecules	Chen et al. (2014)
Chitoson microparticles	Lactoferrin	Chitosan microparticles containing LF were prepared by the without emulsification-solvent evaporation method, and the particle characteristics and release properties in JP second fluid, pH 6.8, were examined	Ch-LF(N) are suggested to be useful for gradual supply to topical diseased sites or for effective delivery to intestinal areas with abundant LF receptors.	Onishi et al. (2007)
Ultradeformable liposomes	Polyphenols from blueberries (Vaccinium myrtillus)	Ethanolic extracts from three blueberry varieties (named Millenia, O'Neal and Blue Crisp) were loaded into ultradeformable liposomes. These nanocarriers are known to be capable of penetrating through the stratum corneum reaching its deeper layers and the viable epidermis	The ethanolic extract-loaded ultradeformable liposomes (nanoberries) from Millenia variety retained an 85% of the antioxidant capacity of the free extract and showed low cytotoxicity on HaCaT cells	Montanari et al. (2013)

Table 9. Comparison between different transdermal drug delivery systems on the basis of various pharamceutical aspects.

Technique	Transport	Sustained delivery	Pain	Cost/ complexity
Chemical enhancer	Good	Moderate	Limited	Good
Iontophoresis	Limited	Good	Moderate	Good
Electroporation	Moderate	Good	Moderate	Limited
Ultrasound	Moderate	Good	Good	Limited
Microneedles	Moderate	Good	Good	Limited
High-velocity particles	Good	Limited	Limited	Limited

Iject: It is capable of delivering drug upto 0.1–1 ml drug and it is needle-free therapy.
Minject: This velocity injector uses polycarbonate syringe which can deliver drug subcutaneously as well as intramusculary.
Cross-ject: This needle-free device uses gas source to propelled drug into subcutaneous tissue with the help of polycarbonate nozzel (Garg, 2012).

Nanocarrier systems

Many techniques have been aimed to disrupt intercellular lipids in an attempt to enhance drug transport across the intact skin. One of the most convenient methods is the use of vesicle formulations as skin delivery systems. Table 8 summarizes various researches carried on novel drug delivery carriers. The rationale behind using vesicles in dermal and transdermal drug delivery is as follows:

- Act as drug carriers into or across the skin (Garg & Goyal, 2014b).
- Act as penetration enhancers for the penetration by altering the intercellular lipids in skin layer (Garg et al., 2012b).
- Serve as a depot for sustained release (Garg et al., 2012a).
- Serve as a rate limiting membrane barrier for the modulation of systemic absorption, hence providing a controlled transdermal delivery system (Garg et al., 2011a). Table 9 represents comparison between different transdermal drug delivery systems based on various pharamceutical aspects.

Marketed products of transdermal patches

Various marketed transdermal patches successfully run in the market. Table 10 represents the various transdermal patches products along with their applications.

Conclusions

Skin permeation enhancement technology is a rapidly emerging field which would expressively increase the number of drugs which is suitable for transdermal drug delivery. Transdermal drug administration route offers many benefits over oral administration of drugs and has stimulated research to find ways to overcome the barrier function of the skin by use of various enhancers' approaches. The exploration for the ideal skin penetration enhancer has been the emphasis of significant research effort over a number of eras. Many potent enhancers have been revealed, but in most of the cases, their effects are associated with toxicity. In recent years, better understanding of the nature of the stratum corneum barrier, interaction of enhancers with the stratum corneum and the development of structure activity relationships for enhancers

Table 10. Marketed products of transdermal patches.

Brand name	Drug	Manufacturer	Indications
Nicotinell®	Nicotine	Novartis	Pharmacological smoking cessation
Matrifen®	Fentanyl	Nycomed	Pain relief patch
Ortho Evra™	Norelgostromin/ethinyl estradiol	ORTHO-McNEIL	Post-menopausal syndrome
NuPatch 100	Diclofenac diethylamine	Zydus Cadila	Anti-Inflammatory
Neupro®	Rigotine	UCB and Schwarz Pharma	Early-stage idiopathic Parkinson's disease
Alora	Estradiol	TheraTech/Proctol and Gamble	Post-menopausal syndrome
Nicoderm®	Nicotine	Alza/GlaxoSmithKline	Smoking cessation
Estraderm	Estradiol	Alza/Norvatis	Post-menopausal syndrome
Climara	Estradiol	3M Pharmaceuticals/BerlexLabs	Post-menopausal syndrome
Androderm	Testosterone	TheraTech/GlaxoSmithKline	Hypogonadism in males
Nitrodisc	Nitroglycerin	Roberts Pharmaceuticals	Angina pectoris
Transderm-Scop®	Scopolamine	Alza/Norvatis	Motion sickness
Nuvelle TS	Estrogen/Progesterone	Ethical Holdings/Schering	Hormone replacement therapy
Deponit	Nitroglycerin	Schwarz-Pharma	Angina pectoris
Nitro-dur	Nitroglycerin	Key Pharmaceuticals	Angina pectoris
Catapres TTS®	Clonidine	Alza/Boehinger Ingelheim	Hypertension
FemPatch	Estradiol	Parke-Davis	Post-menopausal syndrome
Minitran	Nitroglycerin	3M Pharmaceuticals	Angina pectoris
Duragesic®	Fentanyl	Alza/Janssen Pharmaceutical	Moderate/severe pain
Estraderm	Estradiol	Alza/Norvatis	Post-menopausal syndrome
Fematrix	Estrogen	Ethical Holdings/Solvay Healthcare Ltd.	Post-menopausal syndrome
Transderm-Nitro®	Nitroglycerin	Alza/Norvatis	Angina pectoris
Oxytrol®	oxybutynin	Watson Pharma	Overactive bladder
Prostep	Nicotine	Elan Corp./Lederle Labs	Smoking cessation

will aid in optimal characteristics and minimal toxicity. In future, penetration enhancers will play a major role in developing effective transdermal products.

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Declaration of interest

The authors report no conflict of interest.

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