8 Targets in Dermal and Transdermal Delivery and Classification of Penetration Enhancement Methods

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8.1 Introduction

In the past three decades, the skin has gradually become recognized as an important drug delivery route. Being the most accessible organ in the body, the skin can be reached directly and so drug delivery to this tissue is assumed to be relatively easy. There is considerable interest in the skin as a site of drug application for both local (topical) and systemic (transdermal) effect, the first used in the treatment of different skin diseases and the latter as an alternative route for systemic drug administration. Advantages offered by this kind of drug delivery are numerous compared to other conventional routes (Parikh et al. 1984; Guy et al. 1987; Schreier and Bouwstra 1994; Paudel et al. 2010):

1. Transdermal drug delivery systems (TDDS) avoid hepatic first pass which allows for lower doses of drugs to be administered and that means these methods are safer for patients with liver diseases.
2. TDDS avoid the gastrointestinal tract and so bypass problems like drastic pH changes, the deleterious presence of food enzymes, variable transit times and rapidly fluctuating drug plasma concentrations.
3. TDDS are an acceptable, pain-free, non-invasive form of self-administration for patients which ensures easy patient compliance and quick ending of the therapy if necessary.
4. TDDS act as a "depot" controlling the rate of drug input over a prolonged period of time

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and ensuring constant plasma levels even for drugs with short half-times.

In the case of drugs with a narrow therapeutic margin, when applied onto the skin in TDDS, their undesirable side effects are reduced, particularly the effects associated with pulsed peak plasma levels. Furthermore, the dose interval can be reduced.

5. Topical drug delivery systems allow the drug to be directly applied to the skin and delivered to the site of disease in the skin.
6. Topical drug delivery systems like TDDS are non-invasive, avoid hepatic first pass as well as the gastrointestinal tract and problems associated with this drug application route, increase patient compliance and can be self-administered.
7. Specially designed topical delivery systems (like liposomes) may also form drug "depots" in the skin with sustained drug release.

The problems that topical/transdermal drug delivery systems encounter are the low permeability of the stratum corneum which limits the number of drugs available as transdermal products and the potential interaction of drugs with the skin causing irritation and sensitization.

8.2 Therapeutic Target Sites in Topical and Transdermal Drug Delivery

During topical and transdermal drug delivery, drugs are applied to the skin after which they should follow a route to one of the following target sites (Fig. 8.1): (1) the local tissues immediately beneath the application site, (2) deep regions in the vicinity of (but still somewhat remote from) the application site and (3) the systemic circulation (Flynn and Weiner 1991). Therefore, it is important to develop an adequate formulation which delivers the drug to the desired target in the skin or below the skin, i.e. to differ between topical, regional and transdermal drug delivery, since each application has its specific requirements.

Topical delivery can be defined as the application of a drug-containing formulation to the skin to directly treat cutaneous disorders or the cutaneous manifestations of a general disease. Topically delivered drugs should have their pharmacological or other effects confined to the surface of the skin or within the skin (Flynn and Weiner 1991). Formulations designed to target the skin surface include sunscreens, barrier products, cosmetics and insect repellents (Benson and Watkinson 2012). In addition to these, topical formulations can target appendages (hair follicles and sweat pores) and include antiacne products, antiperspirants, hair growth promoters and anti-infectives.

Regional delivery involves the application of a drug to the skin in order to treat diseases or alleviate disease symptoms in tissues that lie deeper, beneath the application site. Pharmacological targets of this type of drug delivery are within the musculature, vasculature, joints and tissues beneath and around the site of application. When targeting regional sites, drug formulations aim to have a regionally selective effect. Regional drug concentrations upon this route of drug administration are higher than the ones achieved by systemic administration (Flynn and Weiner 1991). For both topical and regional drug delivery, systemic absorption is unwanted but unavoidable.

In transdermal delivery drugs are applied to the skin with the aim of reaching the systemic circulation. The purpose of this type of drug delivery is to achieve a therapeutically relevant drug level in order to treat a systemic disease. Hence, the percutaneous absorption of the drug is essential, while the local deposition of the drug is unwanted, but unavoidable (Flynn and Weiner 1991). The use of transdermal delivery is limited to only a small pool of drugs (see Table 8.1) due to the selective barrier properties of the skin. The small number of candidates for this delivery route is a result of the fact that only a few drug molecules have skin permeability coefficients sufficiently high to achieve clinically active plasma levels. Currently, the market for transdermal patches comprises patches with a few low molecular weight drugs: scopolamine for motion sickness, clonidine and nitroglycerin for cardiovascular disease, fentanyl for chronic pain, nicotine to aid smoking cessation, oestradiol (alone or in combination with levonorgestrel or norethisterone) for hormone replacement and testosterone for hypogonadism (Benson 2005).

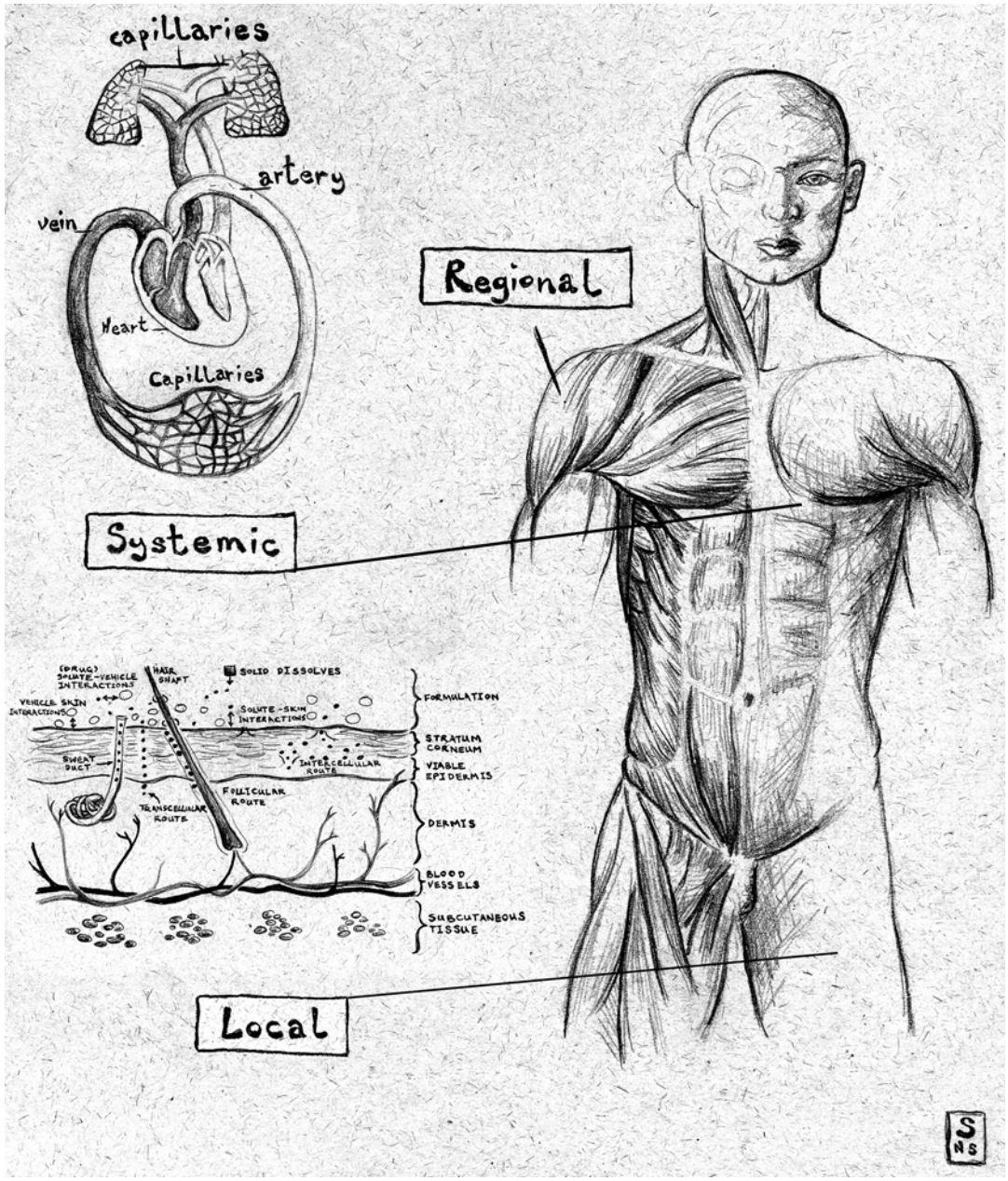

Fig. 8.1 Targets in dermal and transdermal drug delivery

Since percutaneous absorption is pivotal to the effectiveness of both topical and transdermal systems, significant efforts have been devoted to developing strategies to overcome the impermeability of the intact human skin. There are many ways for circumventing the stratum corneum, which provides the main barrier for drug penetration (Barry 2001).

8.3 The Skin

The skin is the largest organ in humans covering approximately 2 m^2 in an average-sized adult. Its main role is to prevent water loss and protect our body from undesired outside influences. This implies that the skin acts as a barrier for diffusion of substances into the

Table 8.1 List of marketed transdermal products

Generic drug	Indication	Product	Manufacturer
1. Scopolamine	Motion sickness	Transderm Scop®	Novartis
2. Nitroglycerin	Angina pectoris	Minitran®, Nitrol®, Transderm-Nitro®, Nitro-Dur®	3 M, Rorer, Novartis, Key Pharms
3. Clonidine	Hypertension	Catapres-TTS®	Boehringer Ingelheim
4. Estradiol	Postmenopausal related symptoms	Estraderm®, Climara®	Novartis, Bayer HealthCare
5. Nicotine	Smoking cessation	Nicoderm CQ®, Habitrol®	Sanofi-Aventis, Novartis
6. Testosteron	Hypogonadism	Androderm®, Testoderm®	Watson Labs, Alza
7. Fentanyl	Analgesia	Duragesic®	Janssen Pharmaceuticals
8. Estradiol and levonorgestrel	Postmenopausal related symptoms	Climara Pro™	Bayer Healthcare
9. Estradiol and norethindrone	Postmenopausal related symptoms	Combipatch®	Novartis
10. Ethinyl estradiol and norelgestromin	Contraception	Ortho Evra®	Janssen Pharmaceuticals
11. Buprenorphine	Analgesia	Bu Trans®	Purdue Pharma L.P.
12. Rivastigmine	Dementia associated with Alzheimer's and Parkinson's disease	Exelon®	Novartis
13. Oxybutynin	Overactive bladder	Oxytrol®, Kentera®	Watson Labs, Orion Pharma
14. Oxybutynin chloride	Overactive bladder	Gelnique®	Watson Labs,
15. Rotigotine	Parkinson's disease	Neupro®	UCB Inc
16. Granisetron	Nausea, vomiting	Sancuso®	ProStrakan Inc
17. Methylphenidate	*Attention deficithyperactivity disorder*	Daytrana	Noven Pharms Inc
18. Selegiline	Depression	Emsam®	Somerset
19. Lidocaine	Postherpetic neuralgia pain relief	Lidoderm®	Teikoku Phar
20. Lidocaine and tetracaine	Local dermal analgesia	Synera®	Zars Pharma
21. Capsaicin	Postherpetic neuralgia pain relief	Qutenza®	NeurogesX
22. Diclofenac epolamine	Topical pain relief	Flector®	Inst Biochem
23. Diclofenac sodium	Topical pain relief in osteoarthritis	Voltaren®	Novartis

underlying tissue (Schaefer 1996; Bouwstra et al. 2003). The main problem in the dermal/transdermal administration of drugs is overcoming this natural barrier (Barry 2001; Bouwstra et al. 2003).

The skin is composed of two anatomically distinct layers: the epidermis and the dermis. Beneath the dermis is the fatty subcutaneous layer hypodermis (See Fig. 8.1). The epidermis is composed of the stratum corneum (10–20 μm thick) and the underlying viable epidermis (50–100 μm), which consists of stratum granulosum, stratum spinosum and stratum basale. The viable epidermis is responsible for the generation of the stratum corneum (Schaefer 1996).

The stratum corneum (horny layer, SC) is the final product of keratinocyte differentiation (cornification). It is made of layers of metabolically inactive cells, embedded in an extracellular matrix of lamellar lipid bilayers. Corneocytes provide the physical and chemical stability of the SC, while the extracellular matrix gives it the

rigid structure, impermeable barrier for water and water-soluble compounds. The SC can be considered as a wall consisting of polyhedric squeeze-protein "bricks" and water-depleted stiff lipid sheets as "mortar" (Ghyczy 2002). The protection of the skin is provided primarily by the SC, which due to its specific structure provides the primary barrier to percutaneous absorption of compounds as well as to water loss (Lindberg and Forslind 2000; Bouwstra et al. 2003). In addition to the stratum corneum, recent findings showed that the viable epidermis is also a rate-limiting barrier to drug penetration (Andrews et al. 2012).

Corneocytes represent cell remnants of terminally differentiated keratinocytes of the viable epidermis. It is the composition of the corneocytes that gives the SC its strong barrier properties. Corneocyte layers are made up of cross-linked proteins and covalently bound lipids. The proteins resist chemical and physical denaturation and the lipids resist solubilization (Schaefer 1996; Downing and Stewart 2000; Williams 2003). In addition to these there is the corneocyte protein envelope which is added during the cornification process (Downing and Stewart 2000). The insoluble cornified envelope is stabilized through core proteins (90 % of its dry mass) cross-linked to the envelope and through covalently bound lipids (10 % of its dry mass) (Schaefer 1996). Therefore, the two layers of the envelope are the layer adjacent to the cytoplasm which is thick and composed of structural proteins and the layer on the exterior of the protein layer which is composed of lipids. The lipid layer serves as an anchor to the keratinocytes and links the proteinaceous domains to the intercellular lipid domains.

Intercellular lipids are arranged in a crystalline sublattice, with only a small portion of lipids in a liquid phase. The crystalline lipid sublattice is far less permeable to water than the liquid lipid phase. The low permeability of the SC is due not only to the unique lipid composition but also to the unique structural organization of the lipid phase (Downing and Stewart 2000; Lindberg and Forslind 2000; Bouwstra et al. 2003; Feingold et al. 1990).

The dermis (or corium) is typically 3–5 mm thick and is the major component of human skin forming the bulk of the skin. It is made of a network of connective tissue, and elastic tissue embedded in a mucopolysaccharide gel (Wilkes et al. 1973). The collagen fibres in the connective tissue give the dermis support and the elastic tissue provides flexibility. The following structures are embedded in the dermis: blood and lymphatic vessels, nerve endings, pilosebaceous units (hair follicles and sebaceous glands) and sweat glands (eccrine and apocrine). Fibroblasts, endothelilal cells and mast cells are present in the dermis, and during inflammation or wound healing, macrophages, lymphocytes and leukocytes may infiltrate (Schaefer 1996). Blood carries the molecules away from near the dermo-epidermal layer, making dermal concentrations of most permeants low. The formed concentration gradient provides the driving force for drug permeation. In addition to blood, the lymphatic system may also remove permeated molecules from the dermis, maintaining a driving force for permeation.

In terms of transdermal drug delivery, the dermis provides a minimal barrier to the delivery of most polar drugs, but may significantly limit the penetration of highly lipophilic molecules (Williams 2003).

8.4 Drug Transport Routes Through the Skin

A molecule placed on the skin surface could reach the viable tissue: (1) via the appendages, (2) across the transcellular route and (3) across the intercellular route (Fig. 8.1).

The transappendageal transport (shunt route transport) involves the transport through the pilosebaceous unit (hair follicles with sebaceous glands) and through sweat ducts. Hair follicles are the most important appendages in terms of surface area (Schaefer 1996). It is generally assumed that this pathway contributes marginally to the steady-state drug flux (Redelmeier and Kitson 1999; Agarwal et al. 2000; Barry 2006). The reason for this is that the skin area covered with the appendages is proportionally smaller than the total skin surface area (Scheuplein 1967).

However, appendages may function as shunts, which may be important at short times prior to steady-state diffusion (Barry 2006). Appendages can contribute to transdermal drug delivery to a varied degree. Some results show that their (appendageal) contribution is small (Siddiqui et al. 1989), whilst others showed that these shunts are indeed important in skin permeation for a range of drugs (Illel et al. 1991). The same author (1997) also suggested that hair follicles and sebaceous glands can be privileged pathways for some molecules or formulations, which enter faster into these shunts than they do through the SC. Changing certain parameters in a formulation (such as pH, solvent, penetration enhancers) can influence follicular drug permeation (Frum et al. 2008). In addition to this some methods used for transdermal permeation enhancement, such as liposomes and iontophoresis, increase the flux of drugs through hair follicles (Li and Hoffman 1997; Hoffman 1998; Ciotti and Weiner 2002). Lauer (1999) reviewed in detail the follicular delivery.

The transcellular route leads directly across the SC, involving the drug transport through keratinocytes and intercellular lipid lamellae. The consecutive partitioning of the drug between hydrophilic (keratine) and hydrophobic (lipids) parts of the SC makes this a difficult pathway. The nature of the permeant and the partitioning coefficient will influence the importance of this route. Hydrophilic molecules may prefer the transcellular route at a pseudo-steady state. However, lipid bilayers are the rate-limiting barrier for permeation via this route (Williams 2003).

The intercellular route is through the lipid bilayers, which comprise around 1 % of the SC diffusional area, yet provide the only continuous phase within the membrane. It is generally accepted that, except for some specialized cases (e.g. highly hydrophilic substances), the intercellular lipid route is the principal pathway by which most small, uncharged molecules traverse the SC (Loth 1992; Abraham et al. 1995; Roberts et al. 1996; van Kuijk-Meuwissen et al. 1998) and many methods for enhancing the drug penetration disrupt or bypass the intercellular lipid bilayers of SC (Barry 2006). According to the domain mosaic model of the skin barrier (Forslind 1994), the structural organization of the lipids of the SC has two phases: (1) lipids in crystalline/gel state surrounded by (2) lipids that form more fluid (liquid) crystalline domains. This second, more fluid lipid domains provide the pathway by which permeants traverse the SC. A method combining ultradeformable lipid vesicles (Transfersomes®) with confocal laser scanning microscopy (CLSM) showed the existence of two different hydrophilic pathways in the SC: an "intercluster" pathway and an intercorneocyte pathway (Schätzlein and Cevc 1998). The intercluster route runs between clusters of 3–10 neighbouring corneocyte "columns". This pathway has low resistance to molecule penetration and it comprises ≤1 % of the total skin surface or ≤20 % of the pathway area in the skin. The intercorneocyte pathway runs between all the corneocytes in a cluster and is therefore very tortuous. This transdermal permeation route resists penetration better and is more abundant (≥3 % of the skin or ≥80 % of the pathway area). Van Kuijk-Meuwissen et al. (1998) showed by CLSM that the liposomally entrapped fluorescent label travelled across SC mainly via the intercellular route.

8.4.1 Factors Affecting Drug Permeation Rate Through the Skin

Factors affecting the drug permeation rate through SC can be considered using the equation (Eq. 8.1) for steady-state flux (Barry 1983):

$$\frac{\mathrm{d}m}{\mathrm{d}t} = \frac{DC_0K}{h} \tag{8.1}$$

where $\mathrm{d}m/\mathrm{d}t$ is the steady-state flux, presenting the cumulative mass of the diffusant, m, passing per unit area through the membrane; C_0 is the constant donor drug concentration; K is the partition coefficient of a solute between membrane and bathing solution; D is the diffusion coefficient; and h is the membrane thickness. From Eq. 8.1, the ideal properties for a molecule in order to penetrate SC well would be the following (Barry 2001; Benson 2005):

- Low molecular mass, preferably less than 600 Da, when D tends to be high.
- Adequate solubility in oil and water in order to achieve a high membrane concentration gradient, which is the driving force for diffusion (C_0 is large).
- High, but balanced (optimal) K, since a too high coefficient may inhibit clearance from viable tissues. This parameter is very important in establishing a high initial penetrant concentration in the first layer of the SC. Molecules showing intermediate partition coefficients (log K octanol/water of 1–3) have adequate solubility within lipid domains of the SC (to permit diffusion through this domain) whilst still having a sufficiently hydrophilic nature to allow partitioning into the viable epidermis.
- Low melting point, which correlates with good solubility as predicted by the ideal solubility theory.

When a drug possesses ideal physicochemical properties (as in the case of nicotine and nitroglycerin), transdermal delivery is feasible. If the drug does not match these ideal characteristics, manipulation of the drug or vehicle to enhance diffusion is necessary and/or penetration enhancement techniques are used.

8.5 Penetration Enhancement Technique Classification

Lots of techniques reported in literature (Barry 2001; Benson 2005; Rizwan et al. 2009) are successful in enhancing the drug delivery into/through the skin. These methods can be grouped initially into chemical and physical methods (Table 8.2). The most extensively studied chemical methods include chemical penetration enhancers (Williams and Barry 2004; Ahad et al. 2009), vesicles (El Maghraby and Williams 2009) and prodrugs (Kasting et al. 1992). Iontophoresis (Costello and Jeske 1995), electroporation (Wang et al. 1998), ultrasound (Cancel et al. 2004) and most recently microneedles (Sivamani et al. 2009) are the most studied physical methods.

Prausnitz and Langer (2008) proposed categorizing TDDS into three generations of development. Drugs in the first generation of TDDS have low molecular weight (Mw), are lipophilic, achieve efficacy at low doses and generally do not require penetration enhancement. The second generation of TDDS utilize enhancement, such as chemical enhancers, iontophoresis and ultrasound but have been limited to the delivery of small Mw molecules. The third generation of TDDS delivers macromolecules to the SC with the help of novel chemical enhancers, electroporation, cavitational ultrasound, microneedles, thermal ablation and microdermabrasion.

8.5.1 Chemical Methods for Penetration Enhancement

Chemical penetration enhancers are defined as agents that partition into and interact with the SC constituents to induce a temporary, reversible increase in skin permeability. These substances temporarily reduce skin resistance and thereby enhance drug flux (Barry 2001). Different groups of structurally related chemical compounds are used as penetration enhancers (see Volume 3, Part 2): water, surfactants, essential oils, terpenes and their derivatives, fatty acids, esters, ethers, Azone and its derivatives, transkarbams, amides, pyrrolidones, sulphoxides and their analogues, etc. (Buyuktimkin et al. 1997; Williams and Barry 2004; Babu and Pandit 2005; Bugaj et al. 2006; Puglia and Bonina 2008; Karande and Mitragotri 2009; Mittal et al. 2009; Brychtova et al. 2010; Ibrahim and Li 2010; Karakatsani et al. 2010; Salerno et al. 2010). Chemical penetration enhancers represent the most studied penetration enhancement method as they have been shown to enhance the topical as well as transdermal delivery of a broad range of drugs both lipophilic and hydrophilic. As an example pyrrolidones enhance permeation of hydrophilic (e.g. mannitol, 5-fluorouracil and sulphaguanidine) and lipophilic drugs (betamethasone-17-benzoate, hydrocortisone and progesterone) (Williams and Barry 2004), as well as terpenes, showing enhanced skin permeation of lipophilic

Table 8.2 Methods used in transdermal penetration enhancement

	Mode of action	Reference
Chemical enhancement methods		
Skin hydration	Increased drug solubility and/or disruption of the SC	Barry (2001)
Chemical penetration enhancers	Increased drug partitioning and/or diffusion in the SC	Williams and Barry (2004)
Vesicles	Drugs are encapsulated into vesicles which interact with the skin	Honeywell-Nguyen et al. (2004)
Prodrugs	Chemical modification of the drug	Qandil et al. (2008)
Ion pairs	Permeation is increased by neutralizing the drug charge with an ion of the opposite charge	Ren et al. (2008)
Salt formation	Drug is changed into a suitable salt form to increase its solubility	Cheong and Choi (2003)
Supersaturated solutions	Thermodynamic activity of the drug solution is shifted, thus increasing penetration rate	Dias et al. (2003)
Eutectic systems	The mixture of drug and another substance lowers the melting point and increases solubility	Ehrenstrom and Reiz (1982)
Physical enhancement methods		
Sonophoresis	Creation of microscopic holes for the transport of drugs	Tezel and Mitragotri (2003)
Iontophoresis	Cavitational ultrasound generates shock waves that disrupt the SC lipid structure	Costello and Jeske (1995)
Electroporation	Electrically driven transport of charged drug molecules	Denet and Preat (2003), Zewert et al. (1999)
Jet injections	Pore formation with short electrical pulses	Bremseth and Pass (2001)
Microneedles	High pressure acceleration of drug particles across the SC	Gill and Prausnitz (2007)
Dermabrasion	Selective removal of the SC by applying high pressure microparticles	Andrews et al. (2011)
Thermal ablation	Short intervals of localized skin heating that creates micropores	Park et al. (2008)
Laser	Thermal ablation of SC creating pores	Gomez et al. (2008)
Waves (radiofrequency, photomechanical, microwaves, photoacoustic)	Disruption of the structure of SC	Levin et al. (2005), Lee et al. (1999), Moghimi et al. (2010), Sa et al. (2013)
Magnetophoresis	Magnetic field is driving drug movement across SC and alters the SC structure	Benson and Watkinson 2012
Combination of techniques		
Chemical enhancers and microneedles, sonophoresis and electroporation		Mutalik et al. (2009), Mitragotri et al. (2000)
Iontophoresis and other physical methods (electroporation, sonophoresis or microneedles)		Hikima et al. (2009), Banga et al. (1999)
Sonophoresis and other physical methods		Mitragotri et al. (2000)
Electroporation and microneedles		Yan et al. (2010)

Table 8.2 (continued)

	Mode of action	Reference
Iontophoresis and chemical penetration enhancers		Wang et al. (2005)
Other methods		
Moxibustion	Increase in skin temperature and skin permeation	Cao et al. (2011)
Submicron injectors	Submicron injection system isolated from sea anemone accelerates the drug across the SC	Shaoul et al. (2012)
Mechanical methods (tape stripping, skin flexing, skin stretching, massage)	Different modes of action: removal of SC layer or reversible formation of micropathways	Rouse et al. (2007), Abdulmajed and Heard (2008), Benson and Watkinson (2012)

drugs, such as ketoprofen (Wu et al. 2001), ibuprofen (Brain et al. 2006), estradiol (Monti et al. 2002), tamoxifen (El-Kattan et al. 2001), zidovudine (Narishetty and Panchagnula 2004), hydrocortisone (El-Kattan et al. 2000) and hydrophilic drugs, e.g. propranolol hydrochloride (Zhao and Singh 1999), bupranolol (Babu and Pandit 2005), nicardipine hydrochloride (Krishnaiah et al. 2002, 2003) and others. Azone and its analogues have been used to enhance a wide range of drugs, too (Afouna et al. 2003; Jampilek and Brychtova 2012). Oleic acid is also widely studied and is one of the leading penetration enhancers used for transdermal applications (Prausnitz et al. 2004).

The limitations of using chemical enhancers are that they are not suitable for enhancing the skin penetration of high Mw drugs and that they often irritate the skin when used at concentrations necessary for achieving useful levels of penetration enhancement (i.e. they have low efficacy at low doses) (Prausnitz et al. 2004). In attempts to solve these problems, researchers have tried synthesizing novel chemical penetration enhancers (Akimoto and Nagase 2003), with optimal enhancer features such as laurocapram (Azone), which safely achieves therapeutic transport enhancement and its analogues (Jampilek and Brychtova 2012), or using two or more penetration enhancers together, because of their synergistic effect in augmenting the penetration of drugs into/through skin (Furuishi et al. 2010).

Barry and co-workers (Barry 1991; Goodman and Barry 1988; Williams and Barry 1991) devised the lipid-protein-partitioning (LPP) theory to categorize chemical penetration enhancers and to describe the mechanism by which they affect skin permeability. According to this theory, enhancers act by one or more of the three modes of action: (1) disruption of the intercellular bilayer lipid structure (lipid modification), (2) interaction with the intracellular proteins of the SC (protein modification) and (3) improvement of partitioning of a drug, coenhancer or cosolvent into the SC (partitioning promotion).

The aforementioned mechanisms of action of enhancers are direct effects of enhancers on the skin. Chemical enhancers can also act indirectly by modifying the formulation. These mechanisms include modification of thermodynamic activity of the vehicle, "drag effect" where the solvent permeating the skin carries the permeant with it and solubilizing the permeant in the donor (Williams and Barry 2004). For more details see Vol. 3 describing a vast range of different chemical penetration enhancers.

Vesicles are colloidal particles, made of water and amphiphilic molecules. The latter form one or more bimolecular layers enclosing an equal number of aqueous compartments. Vesicles can encapsulate hydrophilic drugs within the aqueous regions and lipophilic molecules within the lipid bilayers (Bangham et al. 1965; Williams 2003). There is a large body of research that use different types of vesicles for dermal and transdermal drug delivery (see Volume 2): liposomes, transferosomes, invasomes, ethosomes, niosomes, vesosomes, etc. (Schreier and Bouwstra 1994; Touitou et al. 2000; Cevc et al. 2008; Dragicevic-Curic

et al. 2008, 2009; El Maghraby et al. 2009). The results obtained from these studies are still not consistent and further investigations are needed to fully understand the nature of vesicle transport into/across the skin.

Salt formation is a drug manipulation process where the drug compound is changed into a suitable salt form (Cheong and Choi 2003) with a higher solubility and therefore increased permeation through the skin.

In *ion pair* strategy charged drug molecules penetrate the SC more easily, because the charge on the drug is neutralized by the molecule with the opposite charge, i.e. they form an ion pair (see for details Vol. 1, Chapter 13). In the epidermis the ion pairs dissociate and the drug then diffuses further (Megwa et al. 2000; Ren et al. 2008).

Eutectic systems are a form of penetration enhancement method that uses eutectic mixtures which are drug formulations that combine two substances in an adequate ratio, so that the mixture of substances has a lower melting point than each substance alone (see for details Vol. 1, Chapter 12). The lower melting point of a drug is a parameter that determines the solubility of the drug (see Eq. 8.1) and therefore influences the skin penetration. An example of an eutectic mixture for penetration enhancement is the EMLA® cream (AstraZeneca), being an eutectic mixture of lignocaine and prilocaine (1:1) used as a topical local anaesthetic, which significantly reduced pain associated with venous cannulation in children compared to placebo (Ehrenström-Reiz and Reiz 1982). It was also shown that terpenes form binary eutectic mixtures with ibuprofen and that the resultant melting point depression of the delivery system is correlated with a significant increase in transdermal permeation (Stott et al. 1998). Further, the itraconazole-phenol eutectic formulation enabled, despite the high molecular weight and hydrophobicity of itraconazole, the drug to permeate the skin (Park et al. 2012).

The use of *supersaturated solutions* for enhanced skin delivery of drugs is based on the fact that the maximum, passive flux of a drug across the skin is achieved when it is present in the applied formulation at its saturation concentration, while the drug delivery can further be increased by the creation of a transient, metastable or supersaturated state, whereby the drug's thermodynamic activity is increased above unity (Leichtnam et al. 2006). This approach has the advantage of providing improvement in permeation (proportional to the degree of saturation (DS)) without inducing skin irritation and it is an inexpensive enhancement method. The limitation of the supersaturation approach is its inherent problem of stabilization, and the need to find a way to maintain the metastable state for a period sufficiently long so that an impact on drug transport is apparent (Leichtnam et al. 2007). This period is frequently so short that no impact on transport is observed; however, there are examples of modest to significant effect, like modest increase of transdermal delivery of testosterone (Leichtnam et al. 2006) or significant transdermal delivery of ketotifen (Inoue and Sugibayashi 2012). For more details see Vol. 1, Chapter 11).

Hydration (see for details Vol. 3, Chapter 1) of the SC can enhance the permeation of a large number of drugs used in transdermal delivery, both hydrophilic and hydrophobic (Benson 2005). The mechanisms by which SC hydration increases drug penetration could be by expanding the solubility of the drug and/or by disrupting the structure of the SC due to swelling. The evidence for these mechanisms is not conclusive. In addition to this, hydration does not consistently enhance the penetration of drug molecules and extended occlusion could trigger skin injuries (Bucks and Maibach 1999).

Prodrugs (see for details Vol. 1, Chapter 10) are chemically modified drugs that can cross the skin barrier more easily than the original drug (Sloan et al. 2006). Once the prodrug crosses the SC, an enzymatic and/or chemical transformation will release the active parent drug, which can then exert the desired pharmacological effect. The goal when designing a transdermal prodrug is to alter the physicochemical properties of the drug in such a way as to increase their lipid and aqueous solubility and therefore facilitate the transfer of the drug across the skin. Challenges of the prodrug approach are an increase in size of the modified drug and gaining Food and Drug administration (FDA) approval. In addition to this, many

transdermal prodrug reports still use penetration enhancement techniques (Juluri et al. 2013; Liu et al. 2011; Milewski et al. 2010) showing that this approach is not completely straightforward.

8.5.2 Physical Methods for Penetration Enhancement

Iontophoresis (see for details Volume 4, Part 2) is an electrically assisted delivery to administer therapeutic amounts of the drug across the skin, which enables a significant increase in drug transport across the skin compared to passive drug permeation (even 184-fold; Kalaria et al. 2013). Iontophoresis helps both charged and uncharged drug molecules to migrate across the skin (Costello and Jeske 1995). The penetration enhancing properties of this method are in the electric driving force and not in changing skin permeability. A drug-filled electrode is placed on the skin and a low-voltage current is applied. The mechanisms that move charged and uncharged molecules are electrophoresis and electro-osmosis, respectively (Banga 1998). An advantage of this method is that the drug delivery can be controlled and regulated and application is relatively painless. Limitations of iontophoresis are its relatively high cost, narrow/fixed/restricted drug delivery rates determined by the maximum current applied (Prausnitz and Langer 2008) and molecular size restriction (up to 10–15 kDa) (Kalluri and Banga 2011). Iontophoresis is often used synergistically with other penetration enhancers: chemical penetration enhancers (Wang et al. 2005), ultrasound (Mitragotri et al. 2000) and electroporation (Banga et al. 1999; Alexander et al. 2012). See Volume 4, Part 2 for a detailed explanation of iontophoresis.

Electroporation (see Volume 4, Part 3) is another electrically assisted penetration enhancement method where short pulses of high voltage current are applied to the skin. Skin becomes temporarily permeabilized (the structure of the SC is disrupted) which facilitates the transport of drugs mainly by diffusion and electrophoresis (Denet et al. 2004). Studies show effective penetration enhancement of both small and large molecules by electroporation (Blagus et al. 2013; Denet and Preat 2003; Zewert et al. 1999), but they are at the moment confined to animal models and in vitro studies.

Sonophoresis (Volume 4, Part 1) is the method which uses ultrasound to aid topical and transdermal drug delivery at high (MHz) and low (kHz) frequencies (respectively). Its mode of action is via disturbing the lipid structure of the SC. The mechanisms associated with high- and low-frequency sonophoresis are different; especially, the location of cavitation and the extent to which each process can increase skin permeability are quite dissimilar (Polat et al. 2011). The major effect of low-frequency ultrasound is cavitation, the formation and collapse of air/gas bubbles in the liquid medium at the skin surface (Tezel and Mitragotri 2003). These bubbles oscillate and collapse forming shock waves which induce transient structural changes in the nearby tissue, lipid bilayers of the SC. Cavitational ultrasound can markedly increase drug flux across the skin (Mitragotri et al. 2000) and is non-invasive.

Microneedles are micron-sized needles which can create channels in the skin that penetrate the SC, but do not stimulate the nerves in deeper tissues. In this way drug delivery is increased, pain is avoided and skin invasion is minimal. Microneedles can be solid or hollow and can be used in different ways: piercing of the skin followed by drug-loaded patch; inserting solid microneedles coated with the drug; the drug can be encapsulated in a biodegradable microneedle; or infusion of drug formulation via hollow microneedles into the tissue. Small drugs as well as high Mw drugs, such as peptides, proteins and oligonucleotides, can be transported with this technology (Gill and Prausnitz 2007; Liu et al. 2013). See Volume 4, Chapters 21, 22, and 23 for further reading.

Laser ablation applies laser beams to thermally erode the SC making micropathways in the epidermis (Gomez et al. 2008; Paudel et al. 2010).

During *thermal ablation* skin permeability can be increased when the skin is heated to hundreds of degrees for a very short time, to avoid damage to the surrounding tissues (Park et al. 2008).

The authors suggest that skin changes its permeability upon heating because of the lipid and keratin disruption in the SC, resulting in the removal of SC and formation of microchannels through which a wide range of drug molecules can pass into the deeper layers of the skin. See Volume 4, Chapter 17 for further reading on ablation methods.

Radiofrequency waves can also cause ablation of the SC. Again, microchannels are formed as a result of localized heating (Sintov et al. 2003; Levin et al. 2005). See Volume 4, Chapter 10 for more details.

Microdermabrasion often used in dermatology and cosmetic treatments can also serve as a method for the enhancement of drug penetration into the skin. Removal of the SC is achieved by applying a stream of small crystals. Andrews et al. (2011) showed that microdermabrasion can increase the subcutaneous delivery of insulin in diabetic rats more if the epidermis is removed in addition to the removal of SC. See Volume 4, Chapter 17.

Jet injections are needle-free injections where liquid droplets or solid particles containing a drug are directed towards the skin in a pressurized manner. This high-velocity penetration of particles into or across the skin can be relevant in vaccine administration (Mohammed et al. 2010; Kim and Prausnitz 2011). Insulin can be delivered clinically by jet injection (Engwerda et al. 2011, 2013). See Volume 4, Chapter 15 for more details.

Magnetophoresis (Volume 4, Chapter 13) is a method that uses static magnetic fields to enhance drug penetration (Murthy et al. 2010). Pulsatile electromagnetic fields were used to enhance the penetration of naltrexone in human skin in vitro in a process termed dermaportation (Krishnan et al. 2010; Benson and Watkinson 2012). Dermaportation offers also a potential new delivery method for skin delivery of peptides for a range of dermatological and cosmetic applications (Namjoshi et al. 2008).

The above-mentioned physical enhancement methods can be used in combination; examples are ultrasound and iontophoresis (Le et al. 2000), electroporation and ultrasound (Kost et al. 1996), electroporation and iontophoresis (Banga et al. 1999) and microneedle and iontophoresis (Chen et al. 2009). For a detailed explanation see Volume 4, Chapters 23, 24, and 25.

Conclusion

In the last few decades, the research focus of transdermal drug delivery has been on improving skin permeability through the development of many new methods. Chemical enhancement methods, physical enhancement methods and combination of methods have all contributed to the transdermal industry to a varied degree. A further aim of transdermal systems is to extend the list of products on the market, both in terms of diversity of products and range of indications (diseases) treated. One way forward would be including more macromolecular drug formulations, and the recent method developments are promising to push these boundaries.

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