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Preface

Recently, microneedles have emerged as a significant innovation in medicine, providing a potentially promising alternative to hypodermic injection in the delivery of therapeutic agents. Microneedles have been proven to be painless in human volunteers and can form a microneedle patch, which offers the convenience and safe application of conventional skin patches and the efficiency of hypodermic injection.

Microneedles, varying in needle length, diameter and shape, can be fabricated using techniques, such as microfabrication and moulding. The microneedles can be tailor-made to a length long enough to breach the topmost layer of the human skin, but short enough to avoid the stimulation of the nerves in the underlying skin. The length of the microneedles can also be modified to deliver drugs to specific sites in the skin, such as the immune network, which is an important site of action for vaccines.

The use of microneedles for transdermal drug delivery has developed rapidly in the past decades. However, its real-life application in medicine and cosmetics is still relatively new and less popular compared to other technologies. One goal of this book is to introduce this useful technology, by explaining its application for different purposes, as well as its benefits and safety. We also hope to provide an organized and easy-to-read text for researchers working in related areas.

Tasked with these goals, the book has been written by authors from different academic backgrounds. The first part of the book is written based on Jaspreet Singh Kochhar's doctorate thesis entitled, 'Polymeric Microneedles for Transdermal Drug Delivery', which was completed in 2013. This is followed by a chapter detailing the up-to-date advancement of microneedle technology in the last 5 years.

Dr. Kochhar is now working in industry. Dr. Lifeng Kang, who is now at the School of Pharmacy, The University of Sydney, was his mentor during his Ph.D. tenure and Justin J. Y. Tan and Yee Chin Kwang are students who worked together with them.

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Chapter 1
Introduction & Literature Review

Abstract The skin, commonly considered to be the largest organ of the human body, has been used as a drug delivery route for numerous dermal and transdermal drugs. Being a structural barrier protecting the underlying tissues, the skin poses many challenges to be used as an amenable passage for drugs to permeate. In this chapter, we would describe the current advantages and disadvantages of transdermal drug delivery, making comparisons with different drug delivery routes, elucidate the mechanisms of passive and active transdermal drug delivery and deliberating different formulations which can be delivered via the transdermal route. We would investigate the current status and the development of microneedles, a strategy invented to transiently breach the skin's stratum corneum to deliver drugs through the skin. We would also investigate the different types of microneedles, provide insights into the microneedles used in clinical trials and diffusion cell systems used to assess the efficacy of microneedles in their capacity to deliver drugs through the skin.

Keywords Skin · Route of administration · Transdermal delivery · Microneedle · Diffusion cell

1.1 Drug Delivery Through the Skin

Due to the need of delivering drugs reliably to their intended sites of action, researchers have been looking for patient friendly technologies as the alternatives to conventional oral and parenteral dosage forms. Skin, being the largest organ of the body, has been used as a drug delivery route for local (dermal) and systemic (transdermal) pharmacological effects. The local application of plant extracts and herbal drugs as a treatment of topical conditions such as eczema, dermatitis and psoriasis has been in practice for hundreds of years. Over the past four decades, the potential of the skin as an effective systemic drug delivery route has evolved to be an appealing alternative to the conventional dosage forms. This can be testified by the number of drugs that have been approved by the FDA for transdermal use since the approval of the first transdermal patch in 1979 [1].

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1.2 Skin as a Route for Drug Delivery: Anatomy and Challenges

The primary function of the skin is to provide a rigid structural barrier protecting the underlying tissues rather than being an amenable passage for chemicals to permeate. The skin has three basic layers: epidermis, dermis and hypodermis [2].

Epidermis, the outermost layer of the skin, is comprised of five layers which from top to bottom are as follows: *stratum corneum, stratum lucidum (present only in thick skin), stratum granulosum, stratum spinosum and stratum basale* [2]. The outermost layer of the epidermis, *stratum corneum* (SC), which is also called as the horny layer, presents a strong permeation barrier. The barrier properties of stratum corneum were proved as early as in 1924 by Rein [3] and were supported by several subsequent studies [4–6]. It offers mechanical, anatomical and chemical barrier due to its highly organized multi-layered overlapping cells which are sealed by tightly packed intercellular lipid multi–lamellae [7]. This compacted mass of dead corneocytes interspersed with a lipid rich matrix resembles a "brick and mortar" architecture and is primarily essential to prevent transepidermal water loss, the egress of other endogenous substances and the ingress of foreign particles (chemicals and drugs) [8], maintaining the internal homeostasis of the body. This complex organization of cells and lipids causes hindrance to most pharmacological agents, making it a hurdle for topically administered products to be systemically absorbed. This formidable barrier function of stratum corneum has limited the number of drug candidates which can be delivered through this route and the commercial transdermal products that are available for human use. Tables 1.1 and 1.2 summarize the advantages and limitations of transdermal drug delivery.

Table 1.1 Advantages of transdermal drug delivery

Benefits
The avoidance of hepatic first pass effect and other variables associated with the GI tract, such as pH, gastric emptying time [9, 10].
Sustained and controlled delivery over a prolonged period of time [11].
Reduction in side effects associated with systemic toxicity, i.e. minimization of peaks and troughs in blood-drug concentration [12].
Improved patient acceptance and compliance [13–15].
Direct access to target or diseased site, e.g., treatment of skin disorders such as psoriasis, eczema and fungal infections [16].
Ease of dose termination in the event of any adverse reactions, either systemic or local [8].
Convenient and painless administration [9].
Ease of use may reduce overall healthcare treatment costs [17].
Provides an alternative in circumstances where oral dosing is not possible (in unconscious or nauseated patients) [12].
Effective drug delivery system for drugs with short biological half-lives and narrow therapeutic indices [8].

Table 1.2 Limitations of transdermal drug delivery

Limitations
A molecular weight less than 500 Da is essential to ensure ease of diffusion across the SC [18], since solute diffusivity is inversely related to its size.
Sufficient aqueous and lipid solubility, a log P (octanol/water) between 1 and 3 is required for the permeant to successfully traverse the SC and its underlying aqueous layers for systemic delivery to occur [19].
Intra- and inter-variability associated with the permeability of intact and diseased human skin. This implies that there will be fast, slow and normal skin absorption profiles, resulting in varying biological responses [20]. The barrier nature of intact SC ensures that this route is applicable only for very potent drugs that require only minute concentrations (e.g., 10–30 ng mL^{-1} for nicotine) in the blood for a therapeutic effect [10].
Pre-systemic metabolism; the presence of enzymes, such as peptidases, esterases, in the skin might metabolise the drug into its therapeutically inactive form [21].
Skin irritation and sensitization, referred to as the "Achilles heel" of dermal and transdermal delivery. The skin as an immunological barrier may be provoked by exposure to certain stimuli; this may include drugs, excipients or components of delivery devices, resulting in erythema, oedema, etc. [22–25].

Since skin with its natural barrier properties does not allow the diffusion of many therapeutic molecules, scientists have been working to develop dosage forms and delivery devices that minimally disrupt the skin while enhancing delivery rates. On this aspect, this book describes a novel method of microneedle fabrication and its efficiency in delivering a range of drugs and cosmetics.

1.3 Literature Review

1.3.1 Drug Delivery Systems

A drug delivery system is a formulation or a device that enables the placement of a therapeutic substance in the body and improves its efficacy and safety by controlling the rate, time and place of its release in the body. It is an interface between a patient and a drug. If a device is introduced into a patient's body for functions other than or in addition to delivering a drug, for example, a drug eluting stent, it is strictly classified as a device. Drug delivery systems have been further classified as per the route of administration as described below.

1.3.2 Routes of Drug Delivery

Table 1.3 summarizes various routes of drug delivery. *Oral* route of delivery is most commonly used simply because of the ease of administration and patient acceptance. However, due to the variable absorption through the gut wall, there are some limitations of this route such as enzymatic and acidic degradation of several drugs (particularly biomolecules), first pass metabolism, solubility of drugs in gastric fluid and irritation of gastric mucosa. Also, since the route involves systemic absorption, targeted drug delivery is seldom achieved and may lead to toxicity of nontarget organs as well.

Parenteral drug delivery refers to routes other than the gastrointestinal tract but has been majorly used to refer to injection-based routes such as subcutaneous, intravenous, intra-arterial or intramuscular routes of drug delivery. This route of drug delivery is often used when an immediate effect of the drug is desired and almost 100% bioavailability can be achieved. These injections can be used in comatose and unresponsive patients or those who cannot swallow pills, particularly paediatrics

Table 1.3 Advantages and disadvantages of other routes of administration for systemic drug delivery apart from transdermal

Route of administration	Advantages	Disadvantages
Oral	convenient (portable, easy, painless), economical to the patients (non-sterile, compact), variety (tablets, capsules, liquid, fast, slow release), high dose possible, high surface of absorption, good permeability of GI barrier	may be inefficient (high dose, low solubility), first pass effect (the concentration of a drug is greatly reduced before reaching the systemic circulation), food interaction, local effect (GI flora), not suitable for unconscious patients
Intravenous	direct access to blood central compartment, bypasses the digestive system, does not harm the lungs or mucous membranes, rapid onset of action	increased risk of infection and overdose, risk of the peripheral vein or arterial damage, limited to highly soluble drugs, fear, trained personnel is needed, sustained/controlled action not possible
Subcutaneous	can be self-administered, slow, but generally complete absorption	painful, tissue damage from irritant drugs, max. 2 ml injection
Intramuscular	depot or sustained effect is possible	unpredictable or incomplete absorption, trained personnel is needed
Inhalation	bypasses liver, large surface of absorption	difficulties in regulating the exact amount of dosage, difficulties administering the drug via inhaler
Rectal	bypasses liver, useful for children or older people, drug released at slow, steady state	unpredictable absorption, not well accepted by patients
Sublingual	avoid first pass effect, rapid absorption, drug stability, can be administered for local effect	small dose limit, inconvenience for some patients

and geriatrics. However, trained personnel are required to administer injections, which are associated with pain. Moreover, injections are the biggest risk behind the spread of infections if misused. Achieving a sustained release of the drug via parenteral routes may be a concern and it is difficult to reverse an overdose.

Intranasal route is used for drugs required in small doses and often required to act quickly, through the nasal epithelium, drugs can bypass the blood brain barrier (the protective barrier of cells which restrict the entry of chemicals into the brain) and hence delivery of the drug to the brain can be achieved. Since the drug absorption through nasal mucosa occurs through the aqueous channels of the membrane, the absorption of drug depends on the molecular weight of the compound and its ability to form hydrogen bond with the membrane components. Compounds with molecular weight more than 300 Da do not cross the membrane in significant proportions. Greater nasal secretions and ciliary movements also reduce bioavailability of drugs via intranasal route.

Colorectal drug delivery can be dated back to 1500 B.C., however is not very popular among the consumers as its administration is not very convenient or pleasing. Nonetheless, it is an important route for delivering drugs systemically and locally to the intestines. The drugs can be slowly absorbed for a prolonged action without being affected by the conditions in the gastrointestinal tract. However, hydrophilic drugs are absorbed to a lower extent than hydrophobic drugs. There is a significantly lower first pass metabolism involved via this route.

Pulmonary route of drug delivery has been used since the middle of the twentieth century since the development of aerosols. Recently, this route has been studied for its ability to deliver drugs systemically due to the large surface area available for the exchange of drugs between the lungs and the systemic circulation. However, large molecules such as proteins and peptides do not readily cross the pulmonary mucosa because it is thick, ciliated and covered with mucus lining.

Transdermal drug delivery, as has been described earlier, provides an alternative to the delivery of drugs with small and large molecular weights following the development of various passive and active drug delivery systems. These will be described in greater details in the next section.

1.3.3 Mechanisms of Drug Absorption Through Skin

Delivery of drugs across the skin has been achieved either by passive diffusion or by active disruption of the horny layer (stratum corneum). These strategies increase the efficiency of drug delivery across the stratum corneum in their own capacity. Figure 1.1 describes the various routes of transdermal diffusion employed by different techniques [26].

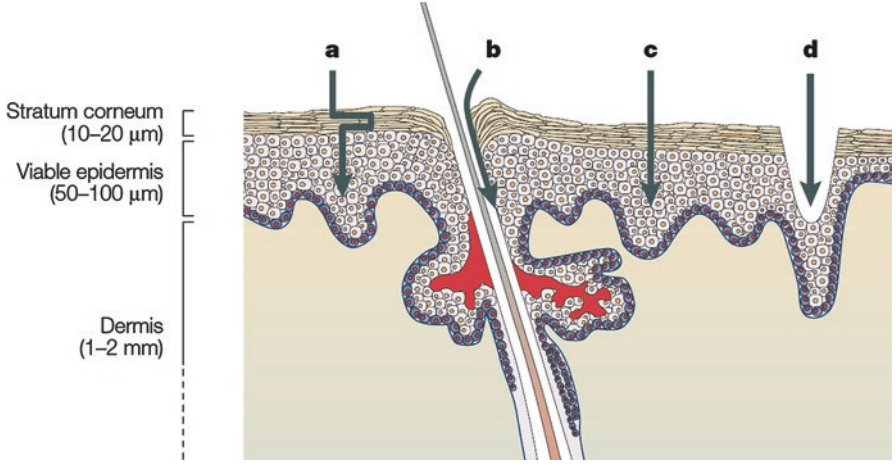

Fig. 1.1 Mechanisms of transdermal delivery (*a*) Transdermal diffusion, passive and with chemical enhancer, follows a tortuous route across the stratum corneum (*b*) Low-voltage electrical enhancement by iontophoresis can make transport pathways through hair follicles and sweat ducts more accessible. (*c*) High-voltage enhancement by electroporation has been shown to occur via transcellular pathways made accessible by disrupting lipid bilayers. The application of ultrasound seems to make pathways (*a*) and (*c*) more permeable by disorganizing lipid bilayer structure. (*d*) Microneedles and thermal poration create micron-scale holes in skin. (Reprinted by permission from Springer Customer Service Centre GmbH: Springer Nature, Nature Reviews Drug Discovery, Current status and future potential of transdermal drug delivery, Prausnitz et al., Copyright 2015)

1.3.3.1 Passive Methods of Transdermal Delivery: Mechanism, Evolution and Limitations

The transport mechanisms by which drugs cross the intact skin have not been completely elucidated, although several pathways have been suggested. Drugs traverse across the intercellular lipids through a complex pathway around the corneocytes, where hydrophilic molecules travel through the polar region (the head group) of the intercellular lipids while the lipophilic molecules traverse through the non-polar chains (the lipid tails) [8, 27]. The appendageal route also involves the passive diffusion of small polar molecules [8].

The passive diffusion of molecules through these routes depends on several factors such as the time scale of permeation, the physico-chemical properties of the permeant (e.g., pKa, stability, molecular size, solubility, partition coefficient, etc.), the integrity and thickness of stratum corneum, density of sweat glands and follicles, skin hydration and vehicle properties [8].

Conventionally, gels, creams and ointments are used as the vehicles for the passive diffusion of drugs across the stratum corneum. Michaels et al. [28] studied the permeation characteristics of several drugs and low molecular weight compounds. The study proved that compounds with a high water and oil solubility and sufficient potency can be delivered through a small area of the skin at an effective rate. This spurred the revolution in transdermal drug delivery and the active research with several potent drugs had led to the development of transdermal patches. Creams and gels have been existing for a long time despite some shortcomings such as a short time of retention on the skin and non-uniform dosing. In 1979, the FDA approved the use of the first transdermal patch to administer scopolamine in the treatment of motion sickness [26]. Transdermal patches have since been developed and marketed for fentanyl, clonidine, nitroglycerin, estrogens, lidocaine, testosterone and the blockbuster nicotine patch, which substantiated the role of transdermal drug delivery in public health. The success of transdermal patches could be testified from the fact that one new patch was approved by the FDA every 7.5 months between 2003 and 2007. It was estimated that the annual market of transdermal patches in the US exceeded US$ 3 billion [26].

Despite this success, the amount of drugs that can be delivered using these conventional passive methods is limited. This can be attributed to the ideal characteristics required for the drugs to be delivered by passive diffusion, i.e. a drug molecular weight of <500 Da, a sufficient lipid solubility and a small therapeutic dose. This is exemplified further as the smallest drug currently incorporated in a commercial transdermal patch is nicotine (162 Da) and the largest is oxybutynin (359 Da) [26]. Drugs with molecular weights larger than 500 Da and a low lipophilicity have failed to achieve the desired bioavailability when delivered passively through the skin. The success of transdermal patches is thus dependent on the judicious selection of drugs which can passively traverse through the skin at therapeutic rates without the aid of physical or chemical disruption of the stratum corneum. Mark Prausnitz and Robert Langer have categorized these as the first generation of transdermal drug delivery systems [27].