Chapter Eight

Transdermal Drug Delivery

INTRODUCTION

The skin, or integument, of the human body both provides protection and receives sensory stimuli from the environment. The skin is the most extensive and readily accessible organ of the body. In an average adult, it covers a surface area of over 2m2 and receives about one-third of the blood circulation; this blood drains into the venous circulation and so avoids first-pass metabolism. It is normally self-regenerating.

Although it is well known that drugs can be applied to the skin for local treatment of dermatological conditions, the advantages of accessibility and the avoidance of first-pass metabolism make it attractive for the systemic delivery of drugs. The objective of a transdermal delivery system is to provide a sustained concentration of drug for absorption, without breaching the barrier function of the skin, and avoiding local irritation. However, the slow transport of many drugs across the skin limits this technique to potent drugs which require plasma concentrations of only a few μg per ml.

Generally, the higher the lipid solubility of a drug and the lower its melting point, the faster it will penetrate the skin. Several drugs can be successfully administered by this route, notably scopolamine, glycerine trinitrate, clonidine and oestradiol. Nicotine patches are becoming common in smoking cessation programs. Nonsteroidal anti-inflammatory drugs (NSAIDs) are also being administered increasingly by transdermal delivery for the treatment of local muscle inflammation. Recently some attention has been focused on the delivery of acetylcholinesterase inhibitors for the treatment of Alzheimer's disease[1]. Other potential candidates are ß-blockers, antihistamines and testosterone.

STRUCTURE OF THE SKIN

The skin is elastic and quite rugged despite the fact that it is only approximately 3 mm thick. It consists of three anatomical layers, the epidermis, the dermis and a subcutaneous fat layer (Figure 8.1).

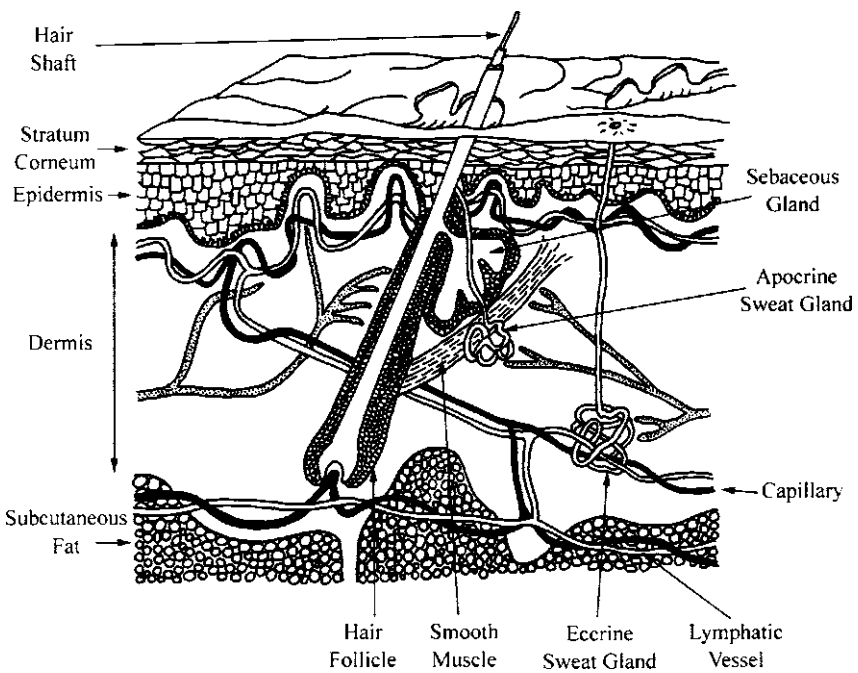

Figure 8.1 Structure of the skin

Epidermis

The epidermis is a thin, dry and tough outer protective outer layer. It forms a barrier to water, electrolyte and nutrient loss from the body, and at the same time is also responsible for limiting the penetration of water and foreign substances from the environment into the body. Damage or removal of the epidermis allows diffusion of small water-soluble non-electrolytes to occur approximately 1000 times faster than in the intact skin[2].

The epidermis is made up of two layers; a basal layer known as the stratum germinativum, which is living, and an outer dead layer called the stratum corneum. The primary cell type in the stratum germinativum is the corneocyte or keratinocyte, which grows from the basal layer outwards to the skin surface. The journey to the surface takes between 12 to 14 days, during which time the cells synthesise the various proteinaceous materials called keratin, they become thin, hard and dehydrated and begin to die. The lifespan of such a cell on the surface is two to three weeks. These cells, together with intercellular lipids synthesized by the keratinocyte, form the outer stratum corneum or horny layer, which is dead. The stratum corneum is the primary protective layer and consists of eight to sixteen layers of flattened, stratified and fully keratinised dead cells. Each cell is about 34 to 44 μm long, 25 to 36 μm wide and 0.15 to 0.20 μm thick, and they are continuously replaced from the basal layer. The water content of the normal stratum corneum is 15 to 20% of its dry weight, but when it becomes hydrated it can contain up to 75% water.

Because the stratum corneum is the main barrier to drug absorption its structure has been closely studied. The most widely used description is the 'bricks and mortar' model (Figure 8.2) in which the keratinocytes form the hydrophilic bricks and the intercellular lipid is the mortar, so that there is a continuous hydrophobic path through the stratum corneum. There is no direct hydrophilic path since the lipid effectively 'insulates' the keratinocytes from each other, and techniques such as electroporation (q.v.) are required to form a continuous hydrophilic path. The lipids consist mainly of ceramides, fatty acids, and cholesterol. Alkanes are commonly present although they are almost certainly derived from environmental sources. It is particularly difficult to study the intercellular lipids since they are easily contaminated with lipids from the sebaceous glands (squalane and triglycerides) or from epidermal fat[3].

The basal layer also contains melanocytes which produce the pigment melanin, which imparts colour to the skin and also protects it from the effects of ultraviolet radiation. Other cells found in the epidermis include Langerhans cells, which play a role in the body's immune defences, and Merkel cells, which are involved in sensory reception. Structures such as hair follicles, nails, and sweat and sebaceous (oil-producing) glands are appendages that develop from the epidermis and extend into the dermis.

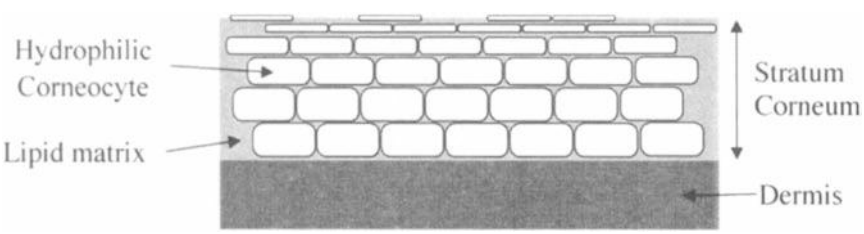

Figure 8.2 Bricks and mortar model of drug absorption through the skin

Dermis

The dermis is a fibrous layer which supports and strengthens the epidermis. It ranges from 2–3 mm thick and in man constitutes between 15% to 20% of the total body weight. The dermis consists of a matrix of loose connective tissue composed of fibrous protein collagen, embedded in an amorphous ground substance. The ground substance consists primarily of water, ions, and complex carbohydrates such as glycosaminoglycans that are attached to proteins (proteoglycans). The ground substance helps to hold the cells of the tissue together and allows oxygen and nutrients to diffuse through the tissue to cells.

There are two distinct layers in the dermis; the papillary layer, which is adjacent to the epidermis, which contains mainly reticulin fibres, with smaller amounts of collagen and elastin, and the reticular layer, which provides structural support since it has extensive collagen and elastin networks, and few reticulin fibres. Elastin is more flexible than collagen and it serves to anchor the epidermis to the dermis, which helps the skin return to its original form after it has been stretched.

The dermis contains blood vessels, nerves, hair follicles, sebum and sweat glands. A deep plexus of arteries and veins is found in the subcutaneous tissue, and this sends out branches to the hair follicles and various glands. A second network of capillaries is located on the sub-papillary region of the dermis. From this plexus, small branches are sent towards the surface layers of the skin. The capillaries do not enter the epidermis, but they come within 150 to 200 μm from the outer surface of the skin. In man, dermal blood flow is approximately 2.5 ml min–1100 g^{-1}, but it can reach 100 ml min–1100 g^{-1} in the fingers.

Three different types of cells are scattered throughout the dermis. These are fibrocytes which synthesize collagen, elastin, and ground substance, histiocytes which are a type of macrophage, and mastocytes, or mast cells which are located near blood vessels; they release histamine in response to irritation, fever, oedema, and pain.

Subcutaneous fat layer

The subcutaneous fat layer acts both as an insulator, a shock absorber, reserve depot of calories and supplier of nutrients to the other two layers. This subcutaneous tissue or hypodermis is composed of loose, fibrous connective tissue which contains fat and elastic fibres. The base of the hair follicles are present in this layer, as are the secretory portion of the sweat glands, cutaneous nerves and blood and lymph networks. It is generally considered that the drug has entered the systemic circulation if it reaches this layer; however the fat deposits may serve as a deep compartment for the drug and this can delay entry into the blood.

Hair and nails

Unlike other large land mammals, humans lack extensive body hair apart from epigamic areas which are concerned with social and sexual communication, either visually or by scent from glands associated with the hair follicles. The hair shaft consists of differentiated horny cells and it is the only part which breaks the surface of the skin. Hair follicles have a diameter of approximately 70 μm and occur at fixed intervals, and hence their separation increases during growth. The density of hair varies over the body surface and it is normally absent from certain areas such as the lips and palms. The extent of hair growth plays an important role in fastening a transdermal delivery system to the skin.

Nails are a modification of the epidermal structure. They are plates of hard keratin which lie along a nail bed, which is composed of modified skin and is very vascular.

Sebaceous glands

Sebaceous glands vary in size from between 200 to 2000 μm in diameter and are found in

the upper third of the hair follicle. Sebaceous glands secrete sebum into the hair follicle, which eventually ends up on the surface of the skin. Sebum consists, on average, of 58% triglycerides, 26% waxy esters, 12% squalene, 3% cholesteryl esters and 1% cholesterol. The lipids maintain a pH of about 5 on the skin surface, and can cause problems for the adhesives in transdermal delivery systems.

Eccrine sweat glands

Eccrine sweat glands are simple tubular glands which possess a coiled section located in the lower dermis. There are approximately 3,000,000 on the body. The normal diameter of the surface opening is 70 μm, but the average width of the ducts are between 5 and 14 μm. They make up 1/10,000 of the total body surface area. Eccrine sweat glands secrete fluid which consists of 99% water with other minor components such as proteins, lipoproteins, lipids and several saccharides. The pH of the secretion is about 5. Apocrine sweat glands are ten times larger than eccrine sweat glands and they open into the hair follicle; however, the apocrine glands secrete a lower volume of sweat than the eccrine glands.

Surface characteristics

The characteristic features of skin change from the time of birth to old age. In infants and children it is velvety, dry, soft, and largely free of wrinkles and blemishes. The sebaceous glands in children up to the age of two years function minimally and hence they sweat poorly and irregularly. Adolescence causes sweating and sebaceous secretions to increase dramatically and the hair becomes longer, thicker, and more pigmented, particularly in the scalp, axillae, pubic eminence, and the face in males. General skin pigmentation increases and acne lesions often develop. As the skin ages, it loses elasticity and exposure to the environment, particularly sun and wind, cause the skin to become dry and wrinkled.

The human skin displays remarkable regional and racial differences, for example, skin of the eyebrows is thick, coarse, and hairy; that on the eyelids is thin, smooth, and covered with almost invisible hairs. Lips are hairless, whilst males have coarse hair over the upper lip and cheeks and jaws. Freckles, also called ephelides (singular ephelis), can also be found on the skin. They are small, brownish, well-circumscribed, stainlike spot on the skin, occurring most frequently in red- or fair-haired people. Freckles do not form on surfaces that have not been exposed to the sun. The ultraviolet radiation in sunlight causes the production of melanin to increase, however, the number of melanocytes remains the same.

The skin is driest at its surface, with a water content of 10 to 25%, and a pH of between 4.2 and 5.6. The lower epidermal layers contain up to 70% water and the pH gradually increases to 7.1 to 7.3. The "acid mantle" derives from the lactic acid and carboxylic amino acids in the sweat secretions mixed with the sebaceous secretions. The lower fatty acids (propionic, butyric, caproic or caprylic) have been demonstrated to have fungistatic and bacteriostatic action, possibly due to the low pH which they produce. The isoelectric point of keratin is between 3.7 and 4.5 and hence materials applied to the skin should have a pH greater than this value.

PASSAGE OF DRUG THROUGH THE SKIN

Model systems for skin

A number of systems are available for studying transdermal drug absorption. In humans, cadaver skin is widely used, as is breast skin from mammary reduction operations. An alternative is the porcine skin model. Pigs have a marked advantage in studies of this type since their sebaceous glands are inactive, which can be particularly useful for the study of epidermal lipids. Large areas of full thickness epidermis can be removed by applying an

aluminium block heated to 60°C for 30 seconds. The hamster cheek pouch also appears to be free of follicles and may be a useful model for absorption studies[4].

There is much interest in drug absorption through the appendageal pathway, but it is hampered by a lack of reliable techniques allowing direct and appendageal absorption to be studied. Hairless rodents still possess underdeveloped follicles, and attempts to study burn scar tissue as follicle-free skin[5] have obvious weaknesses. The Syrian hamster ear is rich in follicles, and a stratification procedure may allow the various routes of absorption to be separated in this model[6].

Routes of absorption

Drug diffusion from a transdermal delivery system to the blood can be considered as passage through a series of diffusional barriers. The drug has to pass first from the delivery system through the stratum corneum, the epidermis and the dermis, each of which has different barrier properties. Differences in composition of these layers cause them to display different permeabilities to drugs, depending on molecular properties such as diffusion coefficient, hydrophobicity, and solubility.

The first limiting factor is the vehicle or device. In a transdermal device, the primary design goal is the maintenance of the desired constant drug concentration at the skin surface for a suitable length of time. This has been achieved with a wide variety of technologies. The second and major barrier for most compounds is the stratum corneum. Skin from which stratum corneum has been removed is highly permeable, while the removed stratum corneum is nearly as impermeable as the entire skin[7]. Skin from cadavers has approximately the same permeability as living skin, suggesting that the underlying tissues present little resistance to drug adsorption[8].

Absorption can occur through several possible routes on an intact normal skin. It is widely accepted that the sebum and hydrophilic secretions offer negligible diffusional resistance to drug penetration. Drug molecules may penetrate not only through the skin but also via the eccrine glands and the sebaceous apparatus; this is known as transappendageal absorption. This route is often neglected since it is difficult to study. The most useful techniques are autoradiography of labelled drugs[9] although several studies have used confocal microscopy with fluorescent drug models. As the openings of glands comprise only a fraction of a percent of the skin surface, transappendageal absorption is often considered unimportant; however it is likely that some materials do penetrate readily by this route. It has been suggested that this route is more rapid than transepidermal transport, and so provides a loading dose, which is sustained by slower diffusion through the epidermis[10].

There are two possible routes of passage of drugs through the stratum corneum; these are via the hydrophilic keratinised cells or the lipid channels organized largely in bilayers between the cells. The lipoidal nature of the lipid channels favours passage of hydrophobic molecules, and since many drugs are hydrophobic, this is their major route of entry[11]. Transdermal drug absorption is influenced considerably by the degree of hydration of the skin, probably due to a combination of several factors including improved contact or wetting, and hydration of the lipid channels of the stratum corneum. Application of oily materials can improve the skin hydration by reducing the evaporation of moisture from underlying tissues. Hydration increases the penetration of polar molecules more than non-polar ones[12] so it is possible that hydration of the lipid channels is more important than hydration of keratinised cells. It is possible to hydrate the lipids in the stratum corneum (despite their hydrophobic nature) because they contain a large fraction of surface-active 'polar lipids' which are surfactant-like in nature (for example, phospholipids), and the phase behaviour of these materials depends strongly on the hydration of their polar groups.

The stratum corneum can act as a reservoir for drugs, causing the pharmacological

response to continue for a short time after the device has been removed. If the skin is then allowed to dry out, the drug will diffuse into underlying tissues more slowly, and application of an occlusive patch which rehydrates the skin can cause release of the drug at a later time.

The final barrier is the living portion of the epidermis and the dermis. Diffusion rates in these viable tissues are much higher than in the stratum corneum and consequently they offer little resistance to absorption. However, the tissues are much more hydrophilic than the stratum corneum, and so act as a barrier to extremely hydrophobic compounds which cannot partition into them. As a result transdermal absorption is optimal for compounds with intermediate polarity which can pass through both the stratum corneum and dermal tissues.

Advantages and disadvantages of transdermal delivery

Drugs applied transdermally avoid the chemically hostile gastrointestinal environment containing acid, food and enzymes. Consequently, this route is useful if there is gastrointestinal distress, disease, or surgery, and one of the first applications of this delivery method was for the treatment of travel sickness. The most attractive feature of transdermal delivery is that first-pass metabolism of the drug is avoided since the blood drains directly into the main venous return. Patient compliance is good since a single device can administer drug for several days, and so is not subject to the problems of multiple daily dosing with tablets. Transdermal devices are usually well accepted, although they can cause irritation to the skin, the degree of which depends both on the drug and the formulation. Finally, the devices have major pharmacokinetic benefits; they can provide a sustained plasma profile over several days, without severe dips occurring at night, and without the potential for dose-dumping which can be a hazard with orally administered sustained release devices. Because the drug is delivered continuously, it can have a short biological half-life. Removal of the device causes the plasma levels to fall shortly thereafter, although some drugs can be stored in the hydrophobic regions of the skin and be released slowly into the blood.

There are however several disadvantages. Drugs may be metabolised by bacteria on the skin surface. Epithelial bacteria can in fact be more prevalent under a transdermal device, since the increased hydration and uniform temperature can encourage growth. Enzymatic activity in the epithelium may be different to that in the gastrointestinal tract, leading to unexpected routes of breakdown of drugs[13]. However, once the enzyme systems are understood they have the potential to activate pro-drugs to active species. It appears that it is possible to influence the metabolism of the drug in the skin by the use of host-guest inclusion complexes; thus for example the incorporation of PGE1 into a cyclodextrin complex reduced the rate of metabolism to other prostaglandins in the epidermis, leading to more efficient delivery[14].

Maintaining contact between a drug delivery device and the skin can present problems. Application of the device occludes the skin, trapping water and sebum from the glands. This, together with the flexing of the skin, can lead to loss of contact and discomfort. The choice of adhesive is restricted since irritation must be minimised, and in early devices, for example those used for clonidine, the drug had to be transported through the adhesive. In many modern devices the adhesive is loaded with drug thus becoming an integral part of the sustained release device. Irritation is often attributed to acrylic adhesives[15]. Silicone-based adhesive disks are a good alternative in this case.

One of the primary functions of the skin is as a protective barrier to foreign agents, and hence it is not surprising that a complex relationship exists between the skin and the body's immune system. A number of cell types (e.g. Langerhans cells and keratinocytes of the epidermis, indeterminant cells, tissue macrophages, mast cells, neutrophilic granulocytes and vascular endothelial cells of the dermis) are directly involved with the immune system

and the transdermal route can cause drug sensitization. If an individual becomes sensitized to drug which has been delivered transdermally, it may become impossible to administer that drug by any other route[16].

Finally, transdermal technology is often uneconomical compared to the simple oral tablet, and so is only used where specific advantages are gained.

FACTORS AFFECTING PERCUTANEOUS ABSORPTION

Individual variation

Individual variation can be as severe a problem as for other drug delivery systems, for example the absorption of hydrocortisone can show nearly a ten-fold variation between individuals[17]. Thus dosage must be titrated to achieve a therapeutic benefit and the transdermal system does have the advantage in this respect that treatment can be stopped rapidly if too great a response is observed. It is straightforward to adjust the dose rate by varying the surface area of the device, although there are obviously practical limits to this.

Age

Skin condition and structure varies with age. The stratum corneum is not fully developed in neonates and this has been used to advantage in the administration of transdermal theophylline and caffeine[18]. It can also pose a major problem since externally applied materials, such as antiseptics and disinfectants, can be absorbed easily. Pre-term infants have very little barrier function, since this does not develop until 9 months after conception. In older people the stratum corneum thickens and is less hydrated, increasing its barrier function.

Site

Drug absorption varies greatly with site of application. Hydrocortisone, for example, penetrates the scrotum 40 times more rapidly than the forearm or back, the commonly used application sites. Heavily keratinised sites, notably the arch of the foot, are several times less efficient than the forearm. This pattern appears to apply to most drugs and offers the interesting possibility of titrating the dose by varying the position of the transdermal device. Patients who experience local irritation may re-site devices, which causes a problem when areas are chosen with very different absorption characteristics. Indeed, recently, it has been suggested that the site of application of the delivery device should be varied to reduce the skin sensitivity[16].

Occlusion

Occlusion increases adsorption considerably in many cases, probably due to increased hydration of the stratum corneum, improving permeability to both polar and non-polar drugs[19]. The increased humidity under the dressing may increase the bacterial load hence potential bacterial degradation of the drug needs to be studied.

Temperature

Temperature affects drug penetration by two mechanisms. Firstly it alters the physiology of the skin, and secondly the physicochemical diffusion rates in the device increase with temperature. The skin temperature is strongly influenced by its surroundings, and may be 20°C cooler than body temperature or several degrees hotter. Fortunately many transdermal patches act as insulators and so the actual variation beneath the device is likely to be significantly lower. The external temperature is more likely to influence the diffusion rate in the controlled release system itself. In disease the body temperature may vary;

temperature-induced variations in the diffusion coefficient may alter the absorption rate by up to a factor of two over this temperature range[20].

Temperature also influences blood flow in the surface vasculature and so might be expected to influence adsorption through this route. However, this possibility has not yet been proven[21] and since the device and the stratum corneum are rate-limiting, the effects of blood flow might be expected to be minimal.

Race

Race appears to influence penetration to a small extent. Negroid stratum corneum has more layers and is generally less permeable, although there is no difference in actual thickness between negroid and European stratum corneum[22]. It is not known if the presence of melanocytes influences the penetration of drugs.

Disease

The skin is the part of the body which comes into direct contact with the environment and hence it is usually the first part of the body to sustain damage or be exposed to irritant substances. Thus, dermatitis is a fairly common complaint. The symptoms generally begin as itching, sweat retention, increased sensitivity and pain, but lead to swelling, oozing, crusting and scaling, with thickening and hyperpigmentation. Inflammation occurs in response to a number of factors e.g. mechanical, chemical, thermal stimuli, infections or imbalance in the autoregulation processes. All these processes can reduce barrier action and lead to increased permeability of the skin to drugs. Allergic contact dermatitis from drugs is a significant obstacle to the development of transdermal drug delivery systems and various animal models are being investigated to test methods for its prevention[23].

Any damaged or diseased area of the skin is likely to display compromised barrier properties and consequently higher drug absorption. Skin permeability is increased in psoriasis and ichthyosis[24 25]. This is unusual since both of these conditions result in thickening of the stratum corneum, but presumably it does not retain structural integrity.

Irritation and inflammation increase penetration even if the skin layer is unbroken[26]; ultraviolet light and sunburn also increase permeability. Burning from more conventional sources such as scalding causes greater penetration, the extent increasing with burn temperature but not apparently with burn duration[27].

VEHICLES AND DEVICES

For topical delivery of drugs, ointments, creams, lotions and gels are used. These materials have a long history but are not suitable for controlled transdermal delivery since they do not provide a protected reservoir of drug or a controlled area of application. There are at least four systems currently employed for systemic delivery of drugs (Figure 8.3). All of these have two main features; a reservoir containing the drug, and a physical mechanism to control the rate at which drug diffuses from the device. The first is the microsealed system, which is a partition-controlled delivery system containing a drug reservoir with a saturated suspension of drug in a water-miscible solvent homogeneously dispersed in a silicone elastomer matrix. A second device is the matrix-diffusion controlled system. The third and most widely used system for transdermal drug delivery is the membrane-permeation controlled system, in which diffusion across a polymer membrane controls the delivery rate. A fourth system, recently made available, is the gradient-charged system[28]. In many formulations the adhesive is spread across the entire face of the device and becomes part of the release rate control. This is considered to be a superior approach to simply using a ring of adhesive around the periphery, because it provides more reliable contact with the skin over the delivery area. The objective in designing all of these systems is to make the release rate from the device rate-

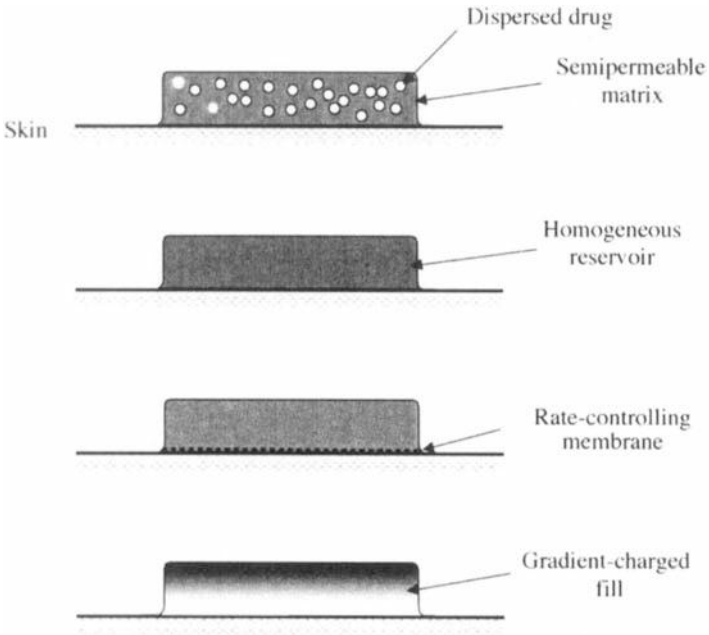

Figure 8.3 Typical devices used for transdermal drug delivery

limiting so that individual physiological variations will not affect the absorption rate. This normally means that only small amounts of drug can be delivered, so the drug must be active in small doses.

The variety of devices, and means for absorption rate control, available is well illustrated by the products available for the transdermal delivery of nicotine, which is one of the most successful applications to date[29]. The Elan ProStep™ patch uses a hydrogel reservoir and absorption is controlled by skin permeability. The Ciba Habitrol™ patch and Cygnus-Kabi Nicotrol™ patch have polymer matrices containing nicotine, and release is controlled by diffusion through the matrix, which is slower than diffusion through the skin. The Alza Nicoderm™ patch also has a matrix reservoir but also uses a polyethylene membrane to control the release rate. This type of device provides protection against the most significant concern of the membrane-controlled devices, that the membrane would become ruptured and dose-dumping would occur. If the drug reservoir is held in a matrix then the release rate of this component can be engineered to be slightly higher than that of the membrane, so that it is not rate-limiting in the intact device, but provides protection in the event of membrane damage.

In the future we can expect to see an increasing number of more sophisticated devices produced by microtechnology. Altea Technologies is currently marketing a Micropor™ system which produces tiny pores of a few micrometres diameter in the stratum corneum using hot-wire technology. Henry et al[30] have reported the use of microfabrication to produce arrays of microneedles which pierce the stratum corneum but are not long enough to trigger pain receptors. Technologies such as these have obvious extensions to delivery by iontophoresis and electroporation.

PENETRATION ENHANCERS

Because transdermal absorption is relatively slow, there has been a large amount of work concerned with finding materials which will increase the penetration rate of drugs through the skin. Such materials are called penetration enhancers. Penetration enhancers are believed to operate by increasing the permeability of the stratum corneum, either in the lipid or the keratinised protein regions. It is unlikely that many materials penetrate as far as the epidermis in sufficient concentration to increase its ability to transport hydrophobic drugs. The largest class of penetration enhancers appear to fluidise the lipid channels. These include dimethyl sulphoxide (DMSO) at high concentrations, decylmethyl sulphoxide, and azone. These materials are known to influence lipid structure[31] but are also polar and capable of swelling proteinaceous regions. Lipid fluidity appears to be the most important factor since at low concentrations substances such as DMSO swell keratin but do not appreciably improve absorption. However, it is only high surface concentrations (>60%) which affect skin lipid fluidity and cause an increase in drug penetration.

Certain penetration enhancers, such as propylene glycol, assist other enhancers to enter the skin. For example, azone is more soluble in propylene glycol than water, so propylene glycol assists its penetration. Additionally, propylene glycol may hydrate keratinised regions of the stratum corneum. Consequently, the azone/propylene glycol mixture is one of the most efficient of currently used penetration enhancers. Isopropyl palmitate combined with triethylene glycol monomethyl ether provides an excellent transdermal flux enhancer *in vitro,* but its effectiveness *in vivo* has not yet been reported[32]. A range of other enhancers of less importance, including fatty acids, esters, urea, and terpenes, have been reviewed by Walker and Smith[33].

Biodegradable enhancers like dodecyl N, N-dimethylamino acetate (DDAA) and N-(2-hydroxyethyl)-2-pyrrolidone have been synthesized to decrease duration of action and toxicity. DDAA and azone caused approximately equal transdermal penetration enhancement of model drugs *in vitro,* but DDAA was less irritant and its irritant effects lasted for only 4 days[34].

A further possibility for penetration enhancement is to influence the nature of the lipid channels by altering lipid biosynthesis in the skin. The intercellular lipid domains of the stratum corneum contain a mixture of cholesterol, free fatty acids, and ceramides. Each of these lipid classes is required for normal barrier function. Selective inhibition of either cholesterol, fatty acid, or ceramide synthesis in the epidermis delays barrier recovery rates after the barrier has been damaged. Possible enhancers using this approach are 5-(tetradecyloxy)-2-furancarboxylic acid which inhibits fatty acid synthesis, and fluvastatin which inhibits cholesterol synthesis. A study by Tsai[35] in hairless mice demonstrated that these two agents in combination could increase the absorption rate of lidocaine by a factor of 8.

Surfactants appear to assist the penetration of polar materials, and it is believed that their mode of action is on the keratinised protein regions of the stratum corneum[36]. It is possible that a combination of hydration and protein conformational change is responsible for this effect. The most powerful surfactants, such as sodium dodecyl sulphate, denature and uncoil keratin proteins, leading to a more porous hydrated structure, through which drugs can diffuse more easily. Such materials also are known to have membrane-solubilizing actions so they probably also influence lipid structure. They are however too irritant for clinical application.

The use of colloidal systems such as liposomes to enhance drug penetration is not particularly successful to date. Conventional liposomes do not appear to pass through intact stratum corneum although there is some evidence that they are phagocytosed by keratinocytes, at least *in vivo,* and so may be taken up in damaged skin where the stratum corneum is broken[37]. A number of authors have examined the possibility that liposomes

may be able to enhance the absorption of drugs by the appendageal route, but these studies are complicated by the difficulty of handling model systems[38]. "Transfersomes" have been used for percutanous delivery in animals and humans[39]. These are liposomes which are constructed from lipid mixtures which are extremely deformable, so that they can squeeze through the pores between the layers of stratum corneum lipid (typically 20–30 nm). The driving force for this penetration is the water activity gradient in the skin; if the skin is occluded so that the water concentration gradient in the stratum corneum is removed, transfersomes do not penetrate.

A number of workers have reported the use of cyclodextrins as penetration enhancers for extremely lipophilic drugs. It is difficult to assess such studies since the cyclodextrin influences the vehicle behaviour as well as that of the skin, and hydrophilic cyclodextrins would not be expected to show significant absorption through the stratum corneum. This area has been reviewed in detail by Matsuda and Arima[40].

The skin will respond to drugs and/or skin permeation enhancers by inflammatory and immune reactions. A fundamental difficulty with the development of penetration enhancers is that an attempt is being made to alter the skin structure; this is almost certain to provoke an irritant reaction. Both sodium dodecyl sulphate and DMSO are irritant; azone is probably the least irritant, partly since it is active at low (1%) concentrations. This problem is made more severe since irritation is often found in transdermal therapy even before penetration enhancers are used.

IONTOPHORESIS

Iontophoresis is the use of an electric current applied to the skin to drive drugs through the epithelium. Iontophoresis enhances transdermal drug delivery by three mechanisms: (a) the ion-electric field interaction provides a directional force which drives ions through the skin; (b) flow of electric current increases the permeability of the skin; and (c) electroosmosis produces bulk motion of the solvent itself that carries ions or neutral species, with the solvent 'stream'. Electroosmosis is the movement of the solvent which occurs when an electric field is imposed near a charged surface. The membrane attracts a predominance of counterions and the movement of these ions in the field causes the solvent to flow in the same direction to maintain the osmotic balance. As both human skin and hairless mouse skin are negatively charged above about pH 4, the adjacent solvent layer contains a predominance of positive ions and electroosmotic flow occurs from anode to cathode. Thus, delivery of positively charged drugs is assisted by electroosmosis, but delivery of negatively charged drugs is retarded[41]. There is evidence that iontophoretic delivery facilitates the deep penetration of drugs compared to direct topical application; for example a study of penetration of lidocaine[42] demonstrated a penetration depth of 10–12 mm compared to 5 mm for direct application.

The effects of electric current on the epithelium have been widely studied but are still incompletely understood[43]. The current does not pass uniformly through the skin, but is largely carried transappendageally via the pores, although some additional pathways open through the lipid channels[44 45]. A number of studies using dyes or tracers have demonstrated that drugs similarly follow these pathways[46 47]. In common with penetration enhancers, electrical enhancement of transdermal drug delivery is limited by similar side-effects, such as tissue damage and pain[43]. Studies of the interaction of penetration enhancers and electrical enhancement suggests that they operate through similar channels, since skin impedance drops substantially after several penetration enhancers are used[48].

A number of factors influence the iontophoretic transport of drugs:

a) The pH of the medium. As the ionization of drugs is controlled by pH, transport is optimum in the pH range in which the drug is fully ionized[49 50] although uncharged species can be carried by the electroosmotic solvent flow[41].

b) The nature of the other ions in the formulation, which compete for transport of the current. These can be ions in the formulation (for example buffers controlling the pH) or endogenous ions such as sodium, potassium, chloride and bicarbonate. The fraction of the total ionic current carried by the drug ion is called the transport number, and it is always less than 1 due to competition from other ions. Consequently when formulating iontophoretic systems, it is important to use a minimum amount of buffer, and choose competing ions with low mobilities (large highly hydrated ions)[51].

c) The current density. The drug flux is proportional to the current density, but the allowable density is limited by safety and patient tolerance to about 0.5 mA cm^{-2}. The working area can be increased but there are practical limits of a few square cm[52].

d) Molecular weight. Larger drugs have lower transport numbers and so are delivered less effectively. This is the major difficulty with the iontophoretic delivery of peptides, which for a time held much promise[53 54]. However, this is partly offset by the need to deliver only extremely small doses of these agents[55]. As the drug size increases, the importance of ionic transport decreases and the drugs become predominantly carried by the electro-osmotic solvent flow[56].

e) Concentration of drug in the delivery system. As the drug concentration at the donor site is increased, the flux across the skin increases[50 52]. This is probably due to the increase in transport number of the drug as its concentration increases relative to that of the competing ions in the system, and so is only significant if the drug is relatively large and has a low transport number. If the transport number is high, then the drug is already carrying the majority of the current and so increasing its concentration will have little effect.

f) Physiological variation. A major advantage of iontophoresis is that a relatively low level of variation in delivery rate is observed. This is probably due to the fact that the applied voltage is adjusted to achieve a specific current, and this will take account of much variability between the subjects due to, for example, site, age, and colour of skin.

g) Waveform of applied current. A number of authors have studied the effect of using AC voltages instead of a steady DC voltage, which can reduce efficiency due to polarization of the skin. Despite these studies there is little agreement about the optimum conditions for delivery[57 58].

ELECTROPORATION

Electroporation (electropermeabilization) is the creation of aqueous pores in lipid bilayers by the application of a short (microseconds to milliseconds) high voltage (200–1000V) electric pulse. It appears that electroporation occurs in the intercellular lipid bilayers of the stratum corneum by a mechanism involving transient structural changes[11]. Although DNA introduction is the most common use for electroporation, it has been used on isolated cells for introduction of enzymes, antibodies, and viruses, and more recently, tissue electroporation has begun to be explored, with potential applications including enhanced cancer tumour chemotherapy, gene therapy and transdermal drug delivery.

As presently understood, electroporation is an essentially universal membrane phenomenon that occurs in cell and artificial planar bilayer membranes. For short pulses (μs to ms), electroporation occurs if the transmembrane voltage reaches 0.5–1.5 V. Due to the small size of the cells it is necessary to apply a much higher voltage to a bulk sample in order to achieve this transmembrane voltage. In the case of isolated cells, the pulse magnitude is 10^3–10^4 V/cm. These pulses cause the formation of pores through the corneocyte which are initially only a few nanometres in diameter but enlarge as the current continues to flow. It is possible that electrical (Joule) heating increases the temperature in the channel sufficiently to melt the skin lipids and increase their permeability, in addition to forming aqueous pores[59]. This is accompanied by a large increase in molecular transport across the

membrane. Membrane recovery can be orders of magnitude slower and cells can remain permeable for several minutes after the pulse or longer. It is likely that, in addition to forming aqueous pores in the skin epithelium, the electric field opens the appendageal route, although the relative importance of these pathways is not yet clear[60]. An associated cell stress commonly occurs, probably because of chemical influxes and effluxes leading to chemical imbalances, which may lead to cell death[61]. A detailed discussion of the electrical and structural changes involved in electroporation is given by Teissié et al[62].

Electroporation has been used to deliver a wide range of drugs with molecular weights up to several thousand daltons[63] and leads to an increase in permeability up to 4 orders of magnitude. Absorption is significantly higher if the field is in the 'forward' direction with respect to the drug being delivered, i.e. if the drug is cationic the electrode should be positive with respect to the skin, and vice versa for an anionic drug.

Combinations of electroporation with iontophoresis[64] and with ultrasound[65] have been demonstrated to provide further increases in drug flux over electroporation alone, and a number of macromolecules also appear to increase flux, possibly by stabilizing the transient pores in the skin[66].

SONOPHORESIS

Low-frequency ultrasound can significantly increase the permeability of human skin to many drugs, including high molecular weight proteins e.g. insulin, g interferon, and erythropoeitin[67]. This effect is termed sonophoresis. Several hypotheses have been proposed as the mechanism by which sonophoresis enhances transdermal drug absorption. These include thermal effects, generation of convective velocities, and mechanical effects. Confocal microscopy indicates that cavitation occurs in the keratinocytes of the stratum corneum upon ultrasound exposure[68]; Wu et al[69] also reported the formation of large (20 micrometre) pores in stratum corneum after exposure to ultrasound. As the ultrasound shock waves pass through the skin, they tear apart the tissue cohesion and create small vacuum bubbles. It is postulated that collapse of these cavitation bubbles induces disorder in the stratum corneum lipid bilayers, thereby enhancing transdermal transport. This seems to be a rather damaging way of increasing permeability, particularly since the stratum corneum is composed of dead cells and so cannot heal itself. Skin electrical resistance measurements support this model. Since transport through the skin is no longer rate limiting after ultrasound treatment, drug transport then depends directly on the diffusion coefficient, and hence molecular weight, of the drug.

Drug absorption can be enhanced by therapeutic ultrasound (frequency: 1–3 MHz and intensity: 0–2 Wcm^{-2}), although typically by a factor of less than 10. Application of lower frequencies at higher powers causes much larger increases in absorption rate, up to a factor of 1000[70]. The absorption rate also depends on the formulation in which the drug is contained, since the drug must diffuse out of its formulation and there is little point in enhancing drug transport in skin if the device is rate-limiting. For example, insulin and vasopressin[71] were better absorbed from saline than from a hydrogel in the presence of an ultrasonic field.

The high powers normally used for sonophoresis may be reduced to therapeutic levels if a permeation enhancer is incorporated in the formulation. Thus Johnson et al[72] studied the penetration of a number of model drugs using combinations of therapeutic ultrasound and penetration enhancers, and were able to demonstrate increases in penetration of two orders of magnitude, depending on the drug/enhancer combination used.

CONCLUSIONS.

Transdermal delivery has a number of advantages which can be of considerable value, most notably the ability to provide uniform plasma levels for considerable periods of time and

avoidance of first-pass elimination. It also has disadvantages which are common to other delivery routes, such as intersubject variability and susceptibility to diseased states at the absorption site. At present, however, its main disadvantage is that only low plasma levels of drug can be maintained, and so it is limited to highly active drugs.

Despite these problems it is currently the optimal route for several compounds, and a number of commercial devices are well-established. It appears that transdermal delivery will be a valuable option in the development of future drug delivery systems.

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