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Topical and Transdermal Drug Delivery

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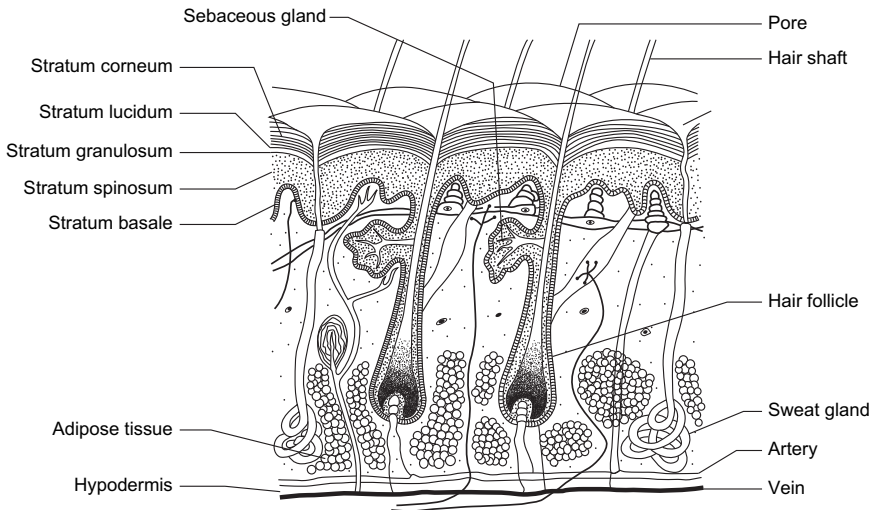
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s0010 1.1 STRUCTURE OF THE SKIN

p0010 Skin is the largest organ of our body, which acts as a protective barrier against the entry of foreign material and possible invasion of pathogens. The skin also prevents the loss of excessive endogenous material such as water (Brown et al., 2006). In addition, the skin serves to reduce the damaging impact of solar UV radiation (Hadgraft, 2004).

p0015 The structure of human skin is portrayed in Figure 1.1. The skin is about 0.5 mm thick and is made up of two distinct layers, the inner dermis and the

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f0010 **Figure 1.1** Anatomy of skin. Transverse section of skin showing different strata and the associated regions in the skin.

overlying epidermis. The dermis that forms the bulk of the skin (1–2 mm thick) is made up of connective tissue elements. Dermis is highly vascular and filled with pilosebaceous units, sweat glands, adipose cells, mast cells, and infiltrating leucocytes (Menon, 2002). The epidermis is avascular in nature, consisting of several types of cells (corneocytes, melanocytes, Langerhans cells, and Merkel cells) and a variety of catabolic enzymes (esterases, phosphatases, proteases, nucleotidases, and lipases) (Jansen and Hopsu-Havu, 1969; Mier and van den Hurk, 1975). The stratified epidermis is about 100–150 μm thick and comprises four distinct layers, namely the stratum basale, stratum spinosum, stratum granulosum, and stratum corneum.

p0020 Stratum corneum is the outermost layer of skin that forms the main barrier for diffusion of the permeants through the skin (Wertz and Downing, 1989). Stratum corneum consists of 18–21 layers of flat, roughly hexagonal cells called corneocytes that are constantly shed and renewed (Menon, 2002). These keratin-rich dead cells, measuring 20–40 μm in diameter, are interspersed within crystalline lamellar lipid matrix to assume a “brick and mortar” arrangement (Elias, 1983). The extracellular lipid contributes 10% of the dry weight of this layer, while 90% is the intracellular keratin. The barrier function of the skin can be attributed to the lamellar lipids that are synthesized in the granular layer and subsequently organized into the extracellular lipid bilayer domains of the stratum corneum (Landmann, 1986). The barrier function of the skin depends on specific ratios of various lipids present and studies reveal that relatively polar lipids

play a critical role in maintaining the barrier integrity of the stratum corneum (Elias et al., 1984; Menon et al., 1986; Elias and Feingold, 1988).

p0025 The viable epidermis is made up of keratinocytes at various stages of differentiation. Lipid catabolic enzymes, namely acid lipase, phospholipase, sphingomyelinase, and steroid sulfatase, are distributed throughout the epidermis, though mainly found in the stratum granulosum and stratum corneum (Menon et al., 1986). The phospholipid content decreases while the sphingolipid and cholesterol content gradually increases as the cells differentiate during their migration to the surface.

s0015 **1.1.1 Dermis and hypodermis**

p0030 The dermis is rich in blood vessels, lymphatic vessels, and nerve endings. Extensive capillary network connects to the systemic circulation with substantial horizontal branching from the arterioles and venules in the papillary dermis. These in turn form plexus and supply capillaries to the hair follicles and the glands. The lymphatic vessels serve to drain the excess extracellular fluid and clear the antigenic materials. The dermis is filled with scattered fibroblasts, macrophages, leucocytes, and mast cells, in addition to the hair follicles, sebaceous glands, and sweat glands. On average, about 10 hair follicles, 15 sebaceous glands, 12 nerves, 100 sweat glands, 360 cm of nerves, and three blood vessels are present in one square centimeter of the skin (Barry, 1983). The hypodermis constitutes the deepest layer of the skin, and consists of the subcutaneous tissue filled with fat cells, fibroblasts, and macrophages.

s0020 **1.2 TOPICAL VS. TRANSDERMAL DRUG DELIVERY**

s0025 **1.2.1 Topical drug delivery**

p0035 Topical drug delivery is the term used for localized treatment of dermatological condition where the medication is not targeted for systemic delivery (Osborne, 2008); examples include treatment of dermatological conditions like eczema or psoriasis by topical application. Examples of drugs delivered topically include corticosteroids, antifungals, antivirals, antibiotics, anti-septics, local anesthetics, and antineoplastics. Topical agents that act by physical action would include protectives, adsorbents, emollients, and cleansing agents, whereas the astringents, irritants, rubefacients, and keratolytic agents are the ones which act by chemical means.

p0040 Conventional topical drug delivery systems include semisolid dosage forms and liquid dosage forms. The semisolid dosage forms include ointments, creams, gels, or pastes, while the liquid dosage forms include lotions

that may be an emulsion, suspension, or a solution (Buhse et al., 2005). Ointments usually contain <20% of water and >50% hydrocarbons, waxes, or polyols as vehicles. Ointments are used as vehicles for topical application of the actives and basically function as skin protective and emollient.

p0045 Creams are emulsion semisolid dosage forms usually containing more than 20% water or volatile components and typically less than 50% hydrocarbons, waxes, or polyols as vehicles (Osborne, 2008). A gel is a semi-solid dosage form that contains a gelling agent to provide stiffness to the dispersion. Gels can be water based (hydrogels) or organic solvent based (organogels) (Gupta and Garg, 2002). A paste can be defined as a semisolid dosage form, containing a large proportion of solids (20–50%) finely dispersed into a suitable vehicle. A lotion may be in the form of a solution or a suspension or an emulsion. Typically these formulations are intended to be applied to the intact skin, generally without any friction.

p0050 An overview of drug delivery systems is shown in Figure 1.2. **AQ1**

s0030 **1.2.2 Transdermal patch systems**

p0055 Transdermal delivery is the term that is confined to a situation in which the drug diffuses through different layers of the skin into systemic circulation to elicit the therapeutic response (Brown et al., 2006). The example would be management of hypertension using a transdermal clonidine patch. In a broader sense transdermal delivery also includes the local anesthetic patches in which the drug is intended to diffuse regionally in the skin to elicit the pharmacological action only in the treated area of the skin. Often, delivery of local anesthesia has been classified under topical drug delivery.

p0060 Transdermal drug delivery systems also termed as “patches” are self-contained discrete dosage forms designed to deliver a therapeutically effective amount of drug through intact skin (Wokovich et al., 2006). Most commercially available transdermal drug delivery systems are of three different types, namely reservoir systems, matrix systems with rate-controlling membrane, and matrix systems without rate-controlling membrane. The reservoir system is made up of three major components, namely the drug



f0015 **Figure 1.2** Transdermal and topical drug delivery.

reservoir, the rate-controlling membrane, and the adhesive. The drug present in the reservoir, along with the other excipients, has to permeate through the rate-controlling membrane before reaching the skin. The adhesive that holds the system in place on the skin can either completely cover the drug release area or only the perimeter around the non-adhering drug release surface. In the matrix type the drug may be embedded in the adhesive matrix. A rate-controlling membrane may be present between the drug-loaded matrix and the adhesive or sometimes the matrix itself can control the rate of release of the actives from the system.

p0065 The drugs that have made it into the transdermal market include scopolamine, nitroglycerine, nicotine, clonidine, fentanyl, estradiol, testosterone, lidocaine, and oxybutinin (Langer, 2004). Recent additions to this list include lidocaine-tetracaine, selegiline, methyl phenidate, and rotigotine. However, the future focus is production of transdermal systems capable of delivering peptides and proteins including insulin, growth hormone, and vaccine across the skin.

s0035 1.3 PERCUTANEOUS ABSORPTION PATHWAYS

p0070 The lipid-rich and structurally complex intercellular region of stratum corneum is said to play an important role in percutaneous absorption (Elias and Friend, 1975). The stratum corneum is known to be selectively permeable and allows relatively lipophilic molecules to diffuse to the lower skin layers (Brown et al., 2006). The transport of such molecules across the stratum corneum barrier is mainly by passive diffusion (Scheuplein and Blank, 1971). The permeation rate through the stratum corneum has been represented by a simple equation (equation (1.1)) (Barry, 1983):

$$\frac{dm}{dt} = \frac{DC_0K}{h} \quad (1.1)$$

p0075 where dm is the amount of the diffusant passed through the membrane in time dt , C_0 is the drug concentration in the donor solution, K is the partition coefficient of the diffusant between the membrane and the solution, D is the diffusion coefficient of the diffusant in the membrane, and h is the membrane thickness. Considering the tortuous intercellular pathway between the corneocytes, the diffusional path length for the permeants is much longer than the thickness of the stratum corneum and is estimated to be $\sim 500 \mu\text{m}$ (Hadgraft, 2004).

p0080 The other potential routes of entry for the permeants from the skin surface to the subepidermal tissues are through the hair follicles with their associated sebaceous glands and via the sweat ducts or through the stratum corneum

between these appendages (Barry, 2001). These follicles passing from the skin surface through the epidermis and reaching the dermis or even the underlying subcutaneous region are the most important appendages of human skin.

s0040 **1.4 APPROACHES TO ENHANCE PASSIVE CUTANEOUS DRUG ABSORPTION**

p0085 For a substance to be well absorbed from the skin it should have a molecular weight of less than 0.6 kDa (Schafer-Korting et al., 2007), a balanced solubility in both oils and water with a log partition coefficient value between 1 and 3 (Hadgraft, 2004). Drug absorption across the skin could be enhanced by adapting one or more of the several strategies discussed subsequently in this chapter.

s0045 **1.4.1 Supersaturation of drug**

p0090 Skin absorption can be enhanced using supersaturated solutions that have greater thermodynamic activity or chemical potentials than the saturated solutions (Hadgraft, 1999). This has been demonstrated based on equation (1.2) proposed by Higuchi (1960):

$$\text{AQ2} \quad \frac{dm}{dt} = \frac{aD}{\gamma h} \quad (1.2)$$

where dm/dt is the permeation rate, a represents the thermodynamic activity of the permeant in its vehicle, D is the diffusion coefficient, h is the membrane thickness, and γ is the effective activity in the skin. The degree of saturation can be increased by increasing the drug concentration in the vehicle or reducing the drug solubility in the vehicle. Thermodynamic activity of saturated solution is unity and a transient increase of the degree of saturation to greater than 1 can be achieved by supersaturation (Moser et al., 2001a). Supersaturation can take place due to water uptake by the skin (Kemken et al., 1992), or by evaporation of a volatile formulation component following application (Coldman et al., 1969; Kondo and Sugimoto, 1987; Kondo et al., 1987a, b; Chiang et al., 1989). Different techniques have been used to produce supersaturated states such as solvent evaporation, mixing of two solvents wherein the drug solubility in one is much more than in the other or by mixing of two solutions of different pH where the solubility is pH dependent. An 18-fold increase in stratum corneum uptake and a 13-fold increase in the flux have been observed with a supersaturated solution of estradiol when compared to a saturated solution that was 18 times less concentrated (Megrab et al., 1995a). The transport of drugs such as hydrocortisone acetate (Davis and Hadgraft, 1991) and piroxicam (Pellett et al., 1994, 1997) has been reported to increase linearly with supersaturation.

The technique has been used recently to increase the permeation of a model lipophilic compound (Moser et al., 2001b).

p0100 Supersaturated solutions are thermodynamically unstable for long-term storage due to drug crystallization. They have been stabilized by addition of polymers, which act as anti-nucleants (Pellett et al. 1997; Schwarb et al., 1999; Ierovolino et al., 2000; Raghavan et al., 2000).

s0050 **1.4.2 Eutectic systems**

p0105 The melting point of a drug influences the solubility and hence the skin penetration. A simple empirical equation (equation (1.3)) that relates the permeability coefficient with the octanol water partition coefficient and the molecular weight of the permeant has been proposed (Potts and Guy, 1992):

$$\text{Log } K_p = -2.72 + 0.71 \log K_{o/w} - 0.0061 \text{ MW} \quad (1.3)$$

where K_p represents the permeability coefficient, $K_{o/w}$ is the octanol–water partition coefficient, and MW is the molecular weight. The permeant melting point was found to be inversely related to the lipophilicity and therefore the transdermal flux for a series of anti-emetics (Calpena et al., 1994). It has been postulated that the lower the melting point of the permeant, the greater is the solubility in a given solvent, including the skin lipids (Benson, 2005). One of the methods by which the melting point of the drug can be reduced is by the formation of a eutectic mixture. A eutectic mixture is a physical mixture of two components that do not interact to form a new chemical substance but at certain ratios inhibit each other's crystallization, resulting in a substance with a lower melting point than either of the components (Stott et al., 1998). A eutectic mixture is formed only when the two components are miscible in the liquid state but remain completely immiscible in the solid state. EMLA cream, a preparation based on a eutectic mixture of lignocaine and prilocaine, is known to provide effective anesthesia for pain-free venepuncture when applied under occlusive conditions (Benson, 2005). Eutectic systems of ibuprofen with terpenes (Stott et al., 1998), ibuprofen with methyl nicotinate (Woolfson et al., 2000), propranolol with fatty acids (Stott et al., 2001), lidocaine with menthol (Kang et al., 2000), and cannabidiol with phosphatidyl choline (Lodzki et al., 2003) have been reported to increase the transdermal permeation. The depression in the melting point to around or below the skin temperature was considered responsible for enhancing the solubility in the skin lipids and thereby the permeability in most of the cases.

s0055 **1.4.3 Prodrug approach**

p0115 Prodrugs have been utilized to enhance the dermal and transdermal permeation **AQ3** of drugs with unfavorable partition coefficients (Sloan, 1989). The prodrug

approach involves addition of a promoiety to increase the partition coefficient and hence the permeation of the parent molecule across the skin. On reaching the viable epidermis, esterases release the parent molecule by hydrolysis of the prodrug. The permeability coefficient of parent compound, indomethacin, has been reported to increase by 100-fold by conversion to an ester prodrug (Jona et al., 1995). The rate of transdermal permeation of the esters through cadaver skin was found to be more than 10-fold higher when compared to the parent drug indomethacin. The effect of prodrug structure on the permeability of levonorgestrel through rat skin has been studied (Friend et al., 1988). The glycidol and haxanediol esters of levonorgestrel were found to partition well into the viable epidermis than the parent compound. The *in vitro* flux values were found to be 20–40 times higher than that of the free drug. Attempts have been made to enhance the intrinsic permeability of 5-fluorouracil by conversion to 1-alkyloxycarbonyl-5-fluorouracil prodrugs (Beall and Sloan, 1996). The ethyl derivative was found to be the most effective, with a 25-fold increase in the flux across hairless mouse skin when compared to 5-fluorouracil (Beall et al., 1994). One of the marketed topical preparations containing the prodrug betamethasone-17-valerate is known to provide a better anti-inflammatory activity than the parent steroid (Benson, 2005).

s0060 **1.4.4 Ion pair formation**

p0120 Charged molecules are poorly permeable across the stratum corneum due to their low lipid partitioning ability. One approach to enhance transdermal permeation is to add an oppositely charged moiety to form a lipophilic ion pair that can partition into the stratum corneum lipids as the charges temporarily neutralize (Barry, 2001). On reaching the aqueous viable epidermis the ion pair dissociates, releasing the parent charged drug, which can partition into the epidermis or dermis and diffuse further (Megwa et al., 2000a, b; Valenta et al., 2000; Stott et al., 2001). Formation of ion pairs with organic acids has been reported to increase the transdermal permeation of indapamide across rat abdominal skin, with lactic acid showing the greatest effect (Ren et al., 2008). The permeation of lidocaine hydrochloride from transdermal films through rabbit ear skin was improved by formation of ion pairs with lauric acid (Padula et al., 2007). However, a mere twofold enhancement was observed in the permeation of propranolol by ion pairing with fatty acids (Stott et al., 2001).

s0065 **1.4.5 Complexation**

p0125 Cyclodextrins are cyclic dextrose polymers that are known to enhance the aqueous solubility and stability of drugs on complex formation. The ring has a hydrophilic surface with a lipophilic core in which organic molecules of appropriate size can be held to form noncovalent inclusion complexes,

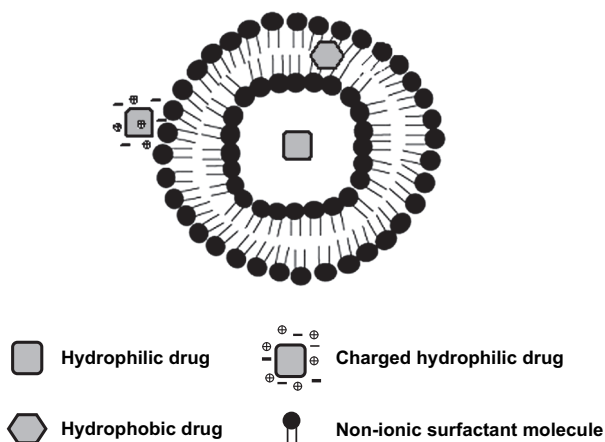
resulting in increased aqueous solubility and chemical stability (Loftsson and Brewster, 1996). Cyclodextrins are macromolecules with a molecular weight of greater than 1000 Da, and therefore not likely to readily permeate the skin. Hydroxypropyl β -cyclodextrin has been reported to increase the *in vivo* percutaneous absorption of liarozole by threefold, while skin pretreatment with an aqueous solution of dimethyl β -cyclodextrin provided a 9.4-fold enhancement (Vollmer et al., 1994). Randomly methylated β -cyclodextrin was found to enhance the permeation of piribedil through hairless rat skin (Legendre et al., 1995). Increased flux across the skin has also been attributed to extraction of stratum corneum lipids by the cyclodextrins (Bentley et al., 1997).

p0130 In contrast, a few studies report a decrease in the skin permeability of the drug after forming a complex with cyclodextrin (Loftsson and Brewster 1996; Williams et al., 1998; Simeoni et al., 2004). The drug permeation is reported to depend on the proportion of cyclodextrin in the complex. A reduced flux was generally seen at relatively higher cyclodextrin concentrations, while higher flux was observed at lower cyclodextrin concentrations (Loftsson and Masson, 2001). It is clear from recent findings that cyclodextrins can only enhance the transdermal delivery when the resistance of the unstirred water layer on the donor side is equal to or greater than the skin resistance (Loftsson et al., 2007). The greatest enhancement on complexation with cyclodextrins was only with smaller lipophilic molecules.

s0070 1.4.6 Liposomes

p0135 Liposomes are colloidal systems comprised of bilayered vesicles made of phospholipids. They may consist of a single (unilamellar) or few (oligolamellar) or many (multilamellar) concentric phospholipid bilayers (Gregoriadis and Florence, 1993). Depending on the size of the vesicles they are further categorized as small unilamellar (SUV) or large unilamellar (LUV) vesicles. Liposomes are capable of encapsulating both hydrophilic and lipophilic molecules in their concentric bilayers, as represented in Figure 1.3. The hydrophilic drugs are usually entrapped in the inner aqueous compartment, while the lipophilic or amphiphilic and sometimes charged molecules are associated with the phospholipid bilayers (Honeywell-Nguyen and Bouwstra, 2005). When the vesicular bilayers are made up of non-ionic surfactants they are termed niosomes. The physicochemical properties like size, charge, lamellarity, and elasticity are governed by the composition of the vesicles. These properties are known to have a significant influence on the effectiveness of liposomes as drug delivery systems.

p0140 Liposomes are used as carriers to deliver the entrapped drugs *into* the skin. They act as permeation enhancers by virtue of the phospholipids that



f0020 **Figure 1.3** Schematic representation of unilamellar vesicle displaying a single lipid bilayer with encapsulated molecules.

penetrate into the stratum corneum and subsequently alter the skin lipid bilayers. They are known to act as a depot for sustained release of actives into the skin, and also modulate the rate and extent of systemic drug absorption (Honeywell-Nguyen and Bouwstra, 2005). Liposomal formulations are known to favor drug deposition in the skin, reduce irritation potential of drugs, and improve drug stability.

p0145 A four- to fivefold higher concentration of triamcinolone acetonide was observed in the epidermis and dermis in addition to lower systemic concentrations with liposomal lotions compared to conventional formulations (Mezei and Gulasekharan, 1980). Similar higher drug concentrations in epidermis and dermis have been observed in comparison to the systemic concentrations with liposomal gel formulations of triamcinolone acetonide (Mezei and Gulasekharan, 1982), progesterone and econazole (Mezei, 1985). The topical delivery of interferon from liposomes constituted with stratum corneum lipids has been reported to be better when compared to water-in-oil emulsion or aqueous solution in a cutaneous herpes simplex guinea-pig model (Weiner et al., 1989).

p0150 The lipid composition, method of preparation, and thermodynamic state of the vesicular bilayers are shown to govern the extent of skin deposition of liposomes (Bouwstra and Honeywell-Nguyen, 2002; El Maghraby et al., 2006). Liposomes constituted with skin lipids were found to be more effective than phospholipid vesicles in delivering drugs to the skin (Egbaria et al., 1990, 1991; Fresta and Puglisi, 1996, 1997; Yu and Liao, 1996; Liu et al., 2004). The reduction in the liposomal cholesterol content increased