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1 Introduction

The absorption of chemicals across the skin has attracted considerable interest in the last decade. Transdermal drug delivery, in particular, has led to the reconsideration of many aspects of the percutaneous penetration process. Most notably, the mechanisms by which molecules penetrate the dermal barrier and the dependence of absorption kinetics and extent upon the physicochemical properties of the permeant have required particular attention (Guy & Hadgraft, 1988).

If one consider the number of compounds which daily come into contact with the skin without causing local or even systemic side effects, one could suppose that skin is impermeable to many substances. In fact local application is the basis of dermatological therapy and the concomitant therapeutic or toxic effect elicited systemically are a direct proof of the permeability of the skin (Schalla & Schafer, 1982). Baker (1985) reported that the thought of the skin been impermeable has changed and the progress achieved in this area clearly demonstrates that the skin is a complex organ and allows the passage of chemicals into and across the skin.

Absorption or transport of drugs, toxicants or other chemicals into or through the skin depends on a number of factors: characteristics of the penetrant, condition of the skin, other chemicals present with the penetrant and external conditions such as temperature, humidity and occlusion. Under most conditions, the factor with perhaps the greatest influence on the rate or extent of skin absorption is the character of the penetrant (Smith, 1990).

Studying the different layers of the skin, the nature of their biochemical and physiological activities and the interaction between barrier elements and penetrants, should indicate how to manipulate the structure of drugs and the pharmaceutical formulation to cause selective and effective permeability. With increased understanding of percutaneous absorption, the advent of singularly effective new topical drugs can be expected. It is thus important to get an overview of the skin itself and particularly physicochemical properties that can influence percutaneous delivery. In this regard a literature study was conducted to investigate the following aspects:

- skin as barrier to percutaneous absorption;
- the process of percutaneous absorption and
- the physicochemical factors influencing percutaneous absorption.

2 The skin as barrier to percutaneous absorption

The skin is the most accessible and probably the most extensive organ of the body. It is well vascularised, elastic and self-regenerating (Lund, 1994). It is a complex organ that serves to protect human from chemical, physical and biological intrusion, while retaining moisture and providing thermal regulation. It consists of three primary regions: the epidermis, the dermis and the hypodermis (Figure 1).

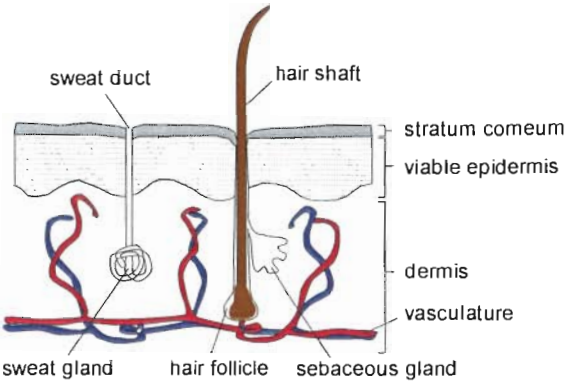

FIGURE 1: Skin features relevant to percutaneous absorption of chemicals (Clifford, 2002).

The human surface is known to contain on the average, 10 – 70 hair follicles and 200 – 250 sweat ducts on every square centimeter of the skin area. These skin appendages however, actually occupy grossly only 0.1 % of the total human skin surface (Chien, 1987). Potts *et al.* (1992) reported that one of the principal roles of the skin is to act as a barrier to the outward transport of water and the inward movement of topically contacting substances. In the context of percutaneous absorption, the barrier to the ingress of molecules is of greatest relevance, although the water-barrier properties are essential for survival. Nevertheless, the mechanistic basis of water-barrier function and percutaneous absorption appears similar. Understanding the development of this barrier can facilitate attempts to enhance percutaneous absorption of drug molecules. Conversely, this knowledge can also be beneficially applied to predict the risk associated with the percutaneous absorption of toxic compounds.

2.1 Stratum corneum

The stratum corneum is the outermost layer of the skin and is the major source of resistance to the permeation of the skin by drug molecules. This coherent membrane, which is 15-20 μm thick over much of the human body, consists primarily of blocks of cytoplasmic protein matrices (keratins) embedded in extracellular lipids. The keratin-containing cells (corneocytes) are arranged in an interlocking structure somewhat akin to brick and mortar. In human, the extracellular mortar consists of a structured complex containing several groups of lipids (Walters, 1990). Figure 2 shows the structure of the stratum corneum.

Lund (1994) documented that the stratum corneum consists of aggregates of closely packed cells, and contains both lipid and aqueous regions. Lipid-soluble drugs can pass readily through lipid regions of the cell membrane whereas water-soluble drugs pass through because of hydrated protein particles within the cell wall. There is some evidence that compounds with both lipophilic and hydrophilic properties, that is with an oil-water partition coefficient close to unity, are best able to pass through the stratum corneum. Water-soluble ions and molecules, unless very small, do not pass through. Gases readily pass through the stratum corneum and this may account for the good penetration found for volatile dugs.

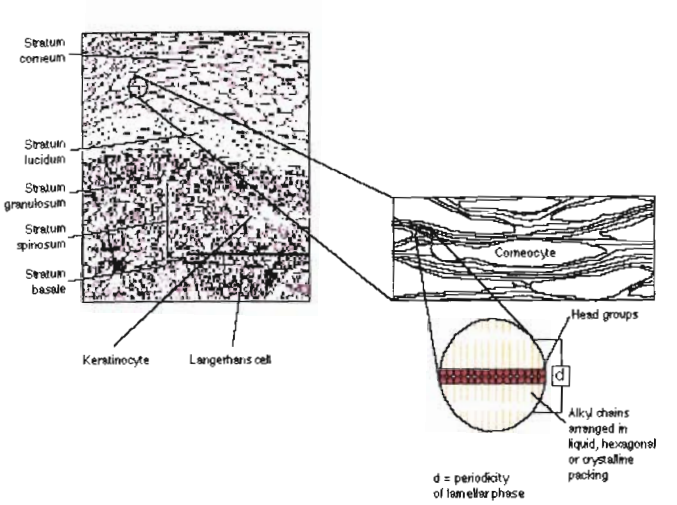

FIGURE 2: Schematic representation of the epidermis of the skin. The structure of the stratum corneum is shown in the inset diagrams (Bouwstra, 1994/5).

The results of several experiments have shown that the stratum corneum is the rate-limiting barrier to the penetration of many chemicals through the skin (Potts *et al.*, 1992). Scheuplein (1976) tape-stripped the skin, thereby removing the stratum corneum and compared the resulting permeability with that of unstripped skin. Removal of the stratum corneum increased the permeability of many solutes by orders of magnitude, strongly implicating the stratum corneum as the primary rate-limiting barrier. The stratum corneum is breached by hair follicles and sweat ducts, which could theoretically provide a low resistance rapid diffusion pathway across the skin This shunt pathway may be significant for extremely slow penetrants such as polar steroids, but the relatively small surface area of the follicles suggests that for most penetrants, dermal permeation dominates except during the period immediately after application (Scheuplein, 1976).

Because of stratum corneum's highly organized structure, it is the major permeability barrier to external materials and is regarded as the rate-limiting factor in the penetration of therapeutic agents through the skin (Foldvari, 2000).

2.2 Viable epidermis

The living cells of the epidermis are located immediately below the stratum corneum. Lying directly above the dermis is a single layer of cells called the stratum basale, which constantly divides to produce keratinocytes. Mitosing cells from the stratum granulosum where they flatten, their content becomes granular and keratin forms. Ultimately, through oxygen and nutrients deprivation, the cells shrinks and die to become the cells of the stratum corneum. Within the stratum corneum, the cells become more compacted as they proceed towards the surface, until they are eventually lost by abrasion (Lund, 1994).

The viable epidermis is often regarded as having properties of an aqueous gel and, as such, does not present a significant barrier to penetration in most circumstances. If the stratum corneum is damaged or if extremely lipophilic drugs are being used, the viable epidermis can act as a rate-limiting factor in percutaneous absorption (Walters, 1990).

2.3 Dermis

Below the epidermis is the dermis or corium. Convolutions in the boundary between the two layers increase the area of contact between the epidermis and the dermis with its numerous blood vessels, nerves and lymphatic, and bring the blood supply closer to the skin surface. The dermis is about 3.2 mm thick and is the largest of the three skin layers. It is predominantly connective tissue and the few cells it contains are principally involved in the secretion of elastin and collagen (Lund, 1994).

Because of the blood vessels approach the interface of the two layers very closely, the dermis cannot be considered as a significant barrier to inward drug permeation *in vivo* (Walters, 1990).

2.4 Subcutaneous fat layer and appendages

The final layer of skin, the subcutaneous fat layer or hypodermis, contain adipose cells which serve principally as an energy source and contribute to the temperature regulation of the skin (Lund, 1994). The dermis supports the appendageal structures, specifically the hair follicles and sweat glands. The pilosebaceous unit comprises of the hair follicle, the hair shaft and the sebaceous gland. The hair follicle is an invagination of the epidermis that extend deeper into the dermis. The lining of the lower portion of the hair follicle is not keratinised and presumably offers a lesser barrier to diffusion than the stratum corneum. With respect to drug delivery, interest in these structures has centered upon the possibility that they may provide "shunt" pathways across the skin, circumventing the need to cross the full stratum corneum. While this is a completely reasonable hypothesis, it is somewhat irrelevant from a practical standpoint because the follicles occupy a relatively insignificant fraction of the total surface area available for transport (~0.1 %). A similar argument can be made with respect to the sweat glands which cover a considerably smaller total area than the follicles. However, appendageal transport may assume a much more important role when specialised transport technology are used to increase dermal delivery (Delgado-Charro & Guy, 2002).

3 The process of percutaneous absorption

Percutaneous absorption is the term used to describe the penetration of a substance (drug or chemical) through the skin and subsequently movement into

the systemic circulation (Lund, 1994). Percutaneous absorption involves the following sequence of events: (1) Partitioning of the molecule into the stratum corneum from the applied vehicle phase, (2) diffusion through the stratum corneum, (3) partitioning from the stratum corneum into the viable epidermis, (4) diffusion through the epidermis and upper dermis and (5) capillary uptake (Figure 2-3). Molecules traverse membranes either by passive diffusion or by active transport (Potts *et al.*, 1992).

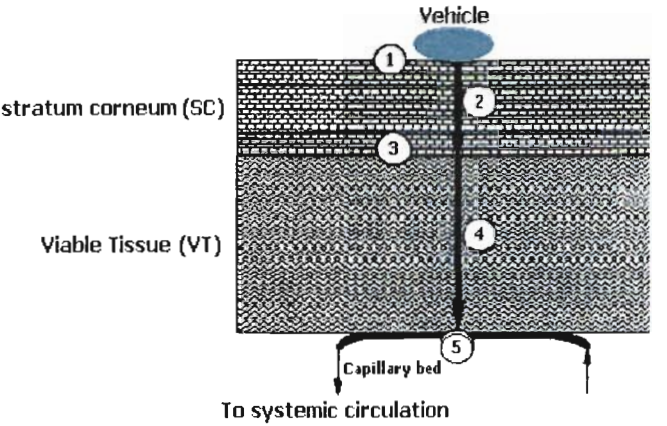

FIGURE 3: The sequential steps involved in percutaneous absorption (Potts *et al.*, 1992).

Passive diffusion, the most important mechanism, requires the compound to be of low molecular weight, to be lipophilic and a concentration gradient must exist. The rate of transport across a membrane by passive diffusion is derived from the classical equation for the First Law of Diffusion of Fick. For drugs that do not meet the requirement for passive diffusion, other transfer mechanism may be operative. In active transport, transfer can be against the concentration gradient and the compound can accumulate in high concentrations. There is energy

requirement for active transport. Two principal absorption routes identified are the transappendageal route and transepidermal route. In transappendageal route the barrier afforded by the stratum corneum is avoided and there is relatively rapid ingress via sweat glands and hair follicles. The transepidermal route corresponds to the diffusion across the stratum corneum. According to Lund (1994), unbroken epidermis constitutes the larger surface for absorption and is widely regarded as the major, but not the exclusive pathway for the percutaneous absorption of many compounds.

The driving force for absorption or transport of any penetrant is proportional to the concentration gradient of that penetrant within the skin (Smith, 1990).

3.1 Routes of penetration

At the skin surface, molecules contact cellular debris, microorganism, sebum and other materials, which negligibly affect permeation. The penetrant has three potential pathways to the viable tissue — through hair follicles with associated sebaceous glands, via sweat ducts, or across contineous stratum corneum between these appendages (Figure 2-4). Fractional appendageal area available for transport is only about 0.1 %; this route usually contributes negligibly to steady state drug flux. The pathway may be important for ions and large polar molecules that struggle to cross intact stratum corneum. Appendages may also provide shunts, important at short times prior to steady state diffusion. Additionally, polymers and colloidal particles can target the follicle. The sebaceous gland cells are more permeable than corneocytes and thus drugs can reach the dermis by entering the follicle (bypassing the invaginated stratum corneum), passing through the sebaceous gland or penetrating the epithelium of

the follicular sheath. The rich blood supply aids absorption, even though the shunt route cross-section area is small (Barry, 2001).

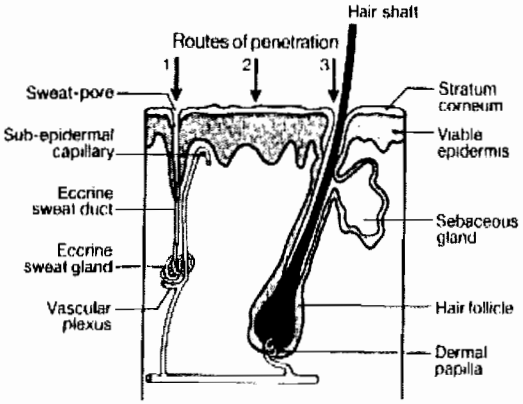

FIGURE 4: Simplified diagram of skin structure and macroroutes of drug penetration: (1) via the sweat ducts, (2) across the continuous stratum corneum or (3) through the hair follicles with their associated sebaceous glands (Barry, 2001).

Figure 5 illustrates the intercellular and transcellular routes of drug permeation through the intact stratum corneum. Because the intercellular space of the stratum corneum was originally assumed to comprise a tiny portion of its overall volume, this space traditionally had been discounted as a possible pathway. Freeze-fracture studies showed, however that the intercellular volume may be a factor of 3 – 7 times greater than previously appreciated and now it is believed to be between 5 and 30 % of the total volume (Elias, 1981).

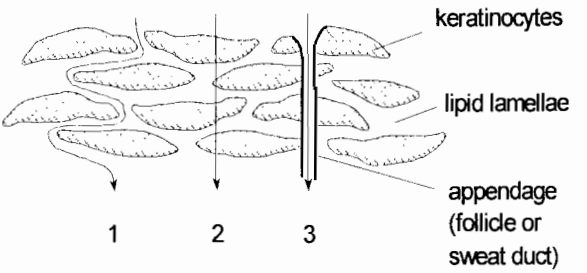

FIGURE 5: Skin permeation routes through the stratum corneum: (1) intercellular diffusion (2) transcellular diffusion and (3) diffusion through appendages (Clifford, 2002).

In a study by Albery and Hadgraft (1979), percutaneous absorption of methyl nicotine showed that this molecule penetrates human skin through the intercellular and not via a transcellular pathway. These observations suggest that the intercellular lipid matrix might be the major rate-determining pathway by which many substances traverse the stratum corneum.

The relative importance of these dual routes for any particular penetrant will depend on several factors, including the chemical potential, the partition coefficient within these protein or lipid regions (Barry, 1987).

3.2 Advantages of percutaneous absorption

The positive features of delivering drugs across the skin to achieve systemic effect can be summarized as follows: Avoidance of significant presystemic metabolism (for example, that due to degradation in the gastrointestinal tract or by liver), and the need, therefore, for a lower daily dose. Drug level can be maintained in the systemic circulation, within the therapeutic window for

prolonged periods of time. Improved patient compliance and acceptability of the drug therapy (Delgado-Charro & Guy, 2002).

4 Physicochemical factors influencing percutaneous absorption

Percutaneous absorption involves the movement of molecules across the epidermal cellular structure. Therefore, factors influencing percutaneous absorption are essentially the same as those influencing gastrointestinal absorption. Additional variables to percutaneous delivery are the condition of the skin, the skin age, the area of skin, the thickness of the barrier phase, species variation and the moisture content of the skin. The primary factors that determine the rate of diffusion through the skin are the physicochemical properties of the drug. Secondary factors are the nature of the vehicle, the pH, the concentration of the drug and the temperature (Idson, 1975).

4.1 Solubility in the stratum corneum

The physicochemical properties of drugs, especially their solubilities, are crucial to decisions about and the design of novel system of delivery (Flynn & Yalkowsky, 1972). Generally, the greater a drug's innate tendency to dissolve, the more likely it is that the drug can be delivered at an adequate rate across any membrane, including the skin. The concentration of drug that can build in the stratum corneum, the skin's principal barrier element, bears some relationship to the solubilities of the drug in organic solvents such as hexane because the diffusion conduit through this barrier is itself lipoidal (Flynn, 1995).

In the formulation of preparations for topical application, it is profitable to select or prepare compounds having the required solubility characteristics before attempting to promote their penetration by pharmaceutical manipulation (Idson, 1975).

In order to permeate through the skin, the molecules need to penetrate from the vehicle into the outermost lipophilic tissue – the stratum corneum. Subsequently, the molecule needs to partition out of the stratum corneum into the essentially aqueous viable epidermis. For very lipophilic molecules the rate-determining step is the partition of the drug from the stratum corneum into the epidermis, whereas for hydrophilic molecules, it is penetration into the stratum corneum. Optimum skin permeation is therefore reached with molecules having "mixed" lipophilic/hydrophilic properties (Surber *et al.*, 1993).

4.1.1 Solubility parameters

A low solubility parameter for a solute is synonymous with high lipophilicity (Roy & Flynn, 1989). A number of studies have suggested that following from the Hiledbrand-Scatchard theory for crystalline solids in regular solution, the permeability, and hence the partition coefficient between the skin and the solvent may be related to the solubility parameter for the solute in the system (Liron & Cohen 1984 and Roy & Flynn, 1989). The solubility parameter of the skin has been estimated as ~10 and therefore drugs, which possess similar values, would be expected to dissolve readily in the stratum corneum (Liron & Cohen, 1984). Thus, penetrants with high solubilities in the stratum corneum will tend to exhibit high fluxes, or at least will not be limited by solubility considerations.

The solubility parameter of an organic solute in the stratum corneum can be estimated from equation 1. If the solubility of the solute in a non-polar organic solvent (like hexane) is known, as well as the heat of fusion and the melting point, and the solubility parameter of the solvent.

$$\ln X_2 = \frac{-\Delta H_f}{RT}\left(\frac{T_f - T}{T_f}\right) + \frac{\Delta C_p}{R}\left[\frac{T_f - T}{T} - \ln\frac{T_f}{T}\right] - \frac{V_2\phi_1^2}{RT}(\delta_1 - \delta_2)^2 \qquad \text{(Equation 1)}$$

Where:

- X_2 is the solute's mole fraction solubility in hexane
- ΔH_f is the heat of fusion
- R is the gas constant
- T_f is the melting point of the solid in degrees Kelvin
- T is any experimental temperature less than T_f
- ΔC_p is the difference in heat capacity between the solid form and the hypothetical supercooled liquid form of the compound, both at the same temperature
- V_2 is the molar volume of the liquid solute
- Φ_1 is the volume fraction of the solvent
- δ_1 is the solubility parameter or square-root of the cohesive energy density of the solvent (hexane)
- δ_2 is the solubility parameter or square-root of the cohesive energy density of the solute.

Roy & Flynn (1988) assessed the solubilities of the narcotics (morphine, hydromorphine, codeine, fentanyl, sufentanil and meperidine) in selected solvents i.e hexane and water. As the prototypical narcotic, morphine's solubilities in solvents of wide-ranging polarity have been characterized and these established an overall picture of the solubility behaviour of the class. The solubility parameter (δ_2) of morphine calculated from its solubility in hexane and its heat of fusion was virtually identical to the best-fit solubility parameter obtained from the solubilities in all London solvents. This was in agreement with

the work of Neau and Flynn, which demonstrated that the solubility parameters of alkyl *p*-aminobenzoates can be determined accurately and with a deviation of no more than ± 0.2 $(cal/cm^3)^{1/2}$ from their solubilities in *n*-hexane or *n*-heptane and their heat of fusion and melting points.

Roy & Flynn (1988) found a monotonic relationship with δ_2 and octanol-water partition coefficient (K_{oct}) for six narcotic alkaloids. For solutes with log K_{oct} less than –1, the δ_2 was constant at about 9.5. Above this value of log K_{oct}, δ_2 increased sharply. Maximum permeability coincided with a δ_2 of 9.6 – 9.8 in a plot of log K_{oct} against the square root of δ_2. The observed decrease in permeability coefficient with further increase in δ_2 corresponds to a dependence of permeability on lipophilicity.

4.1.2 Aqueous solubility

The solubility of the penetrant in the various phases present in the skin and its surrounding plays a large part in determining the rate of penetration. In a typical case, the penetrant will be present on the skin surface either dissolved in or dispersed in a vehicle of some sort. While it is the concentration of penetrant within the skin that controls the rate of transport, that concentration is dependent on the concentration and solubility of the penetrant in the vehicle on the skin surface. It should be pointed out that once the penetrant has crossed the stratum corneum, it must partition into the underlying layers of epidermis, dermis and circulatory system. These tissues are typically more hydrophilic than is the stratum corneum and can present a barrier to transport of extremely hydrophobic penetrants (Smith, 1990).

The stratum corneum, which is the rate-limiting biological barrier to percutaneous absorption, is considered to be lipophilic in nature, dermal delivery of a drug

requires that the drug exhibit significant lipid solubility. However the drug must also exhibit some appropriate degree of water solubility in addition to its lipid solubility, in order to partition into and through at least the initial hydrophilic macrophages of the lipophilic stratum corneum and in addition, solubility of drug in the internal aqueous phases is essential for it to express its systemic potency (Beall, 1993).

Modification of molecular structure to change the partitioning and solubility characteristics of the compound can alter the rate of penetration through the epidermis has been used extensively for corticosteroids. As a general rule, for good absorption the drug should have an oil-water partition coefficient close to unity and a moderately high water solubility. Among many esters of betamethasone tested, the highest topical activity was found for the 17-valerate esters, which exhibited this properties (Lund, 1994).

The study of Fourie (2001), found that N-methyl and N-ethyl analogues of carbamazepine have higher aqueous solubility (25°C & 32°C) than carbamazepine itself and this parameter was in agreement with the partition coefficients and steady state flux of these analoques. Cordero *et al.* (1997) investigated the *in vitro* penetration of a series of nonsteroidal anti-inflammatory drugs (NSAID) across excised human skin. Selected physicochemical parameters were experimentally determined; this includes the experimental solubilities in buffer at pH 6.6 and in water. Significant differences were found in flux values of the various NSAIDs. Ketoproven exhibited the highest flux, followed by ketorolac and aceclofenac. The high trandsdermal fluxes of ketoprofen and ketorolac are associated with their intrinsic solubilities together with their moderately high k_p values.

Beall (1994) studied the dermal delivery of 5-fluorouracil (5-FU) by 1-alkyloxycarbonnyl-5-FU prodrugs. The results from the diffusion cell experiments show that changes in the promoiety that result in increase water solubilities of more lipid soluble derivatives lead to increased rates of delivery of the total 5-FU species through the skin. There is a good correlation between water solubility and flux within the series of more lipid soluble prodrugs. The most water-soluble member of the series is the most effective member at enhancing flux (Beall, 1994).

The activities of highly water-soluble and highly oil-soluble molecules are less than those of drugs with a more evenly balanced solubility behaviour (Lund, 1994).

4.2 Diffusion coefficient

Barry (1988) defined "diffusion coefficient" (D) as the measure of how easily a molecule diffuse through the stratum corneum. The diffusion coefficient of a drug in the skin is dependent on properties of the drug and the medium through which it diffuses. One drug property which is well documented as having a major influence on the diffusion coefficient is that of molecular size and mass. Another important parameter which has been documented is the drug state, e.g. ionised or nonoinsed, with nonionised forms diffusing more freely than ionised forms.

Chemicals are transported into and through the skin by a solution-diffusion process. The penetrant must dissolve in the skin, diffuse across the skin and partition into the body fluids or tissues beneath the skin. Due to the extraordinary barrier that skin represents to most penetrants, diffusion across the skin is typically the slowest and therefore rate-controlling step in this process. In this

case, the rate of transport across the skin can be described by the following approximation of Fick's first law (Smith, 1990):

$$J = \frac{D\Delta C_m}{\ell} \qquad \text{(Equation 2)}$$

Where:

J is the flux of penetrant across the skin ($g/cm^2/s$)

D is the diffusivity of the penetrant in the skin in cm^2/s

ΔC_m is the difference in penetrant concentration within the skin in g/cm^3

ℓ is the thickness of the skin in centimeters.

In the simplest sense, the skin can be considered as a bilaminate membrane consisting of adjacent lipoidal and aqueous layer. Transport through this structure, assuming that the permeant exists at unit activity on the stratum coneum surface, is governed by two diffusion coefficients (D_s, D_v), two associated diffusion path lengths (l_s, l_v), and a partition coefficient (K) of the penetrant between stratum corneum and viable tissue (Figure 2-6).

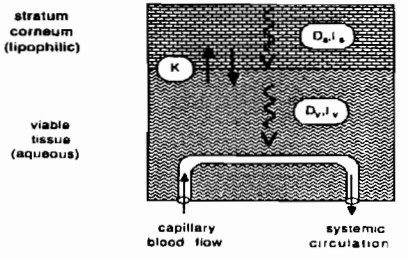

FIGURE 6: Schematic representation of skin as a bilaminate membrane. Diffusion coefficient and diffusion path lengths through the adjacent layers are indicated (Guy & Hadgraft, 1988).

The value of l_s reflects the distance from the top to the base of the stratum corneum, l_v is the distance from the base of the stratum corneum to the upper dermal capillaries, D_s is the characteristic diffusion through the stratum corneum and D_v is the characteristic diffusion through an aqueous protein gel (Guy & Hadgraft, 1988).

For typical small polar molecules such as water and the alcohols, the reported diffusion coefficient in stratum is of the order of 10^{-10} to 10^{-9} cm^2sec^{-1} (Table 1).

TABLE 1: Approximate permeability data for various homologous series penetrating through skin (Barry, 1983).

Penetrant	Diffusion coefficient (cm^2sec^{-1})
C4 Series:	
Ethyl ether	10^{-9}
2-Butanone	10^{-9}
1-Butanol	10^{-9}
2-Ethoxyethanol	10^{-10}
2-3-Butanedoil	10^{-9}
Alcohols:	
Ethanol	10^{-9}
Pentanol	10^{-9}
Octanol	10^{-9}
Steroids:	
Progesterone	2×10^{-11}
Cortexone	2×10^{-11}
Cortexolone	4×10^{-12}
Cortisone	1×10^{-12}

Cortisol	3×10^{-3}

The speed with which materials diffuse depends first and foremost on the state of matter of the diffusing medium. In gases and air, typical diffusion coefficients are large (on the order of 0.05 – 1.00 cm^2sec^{-1}) because the free volume or void space available to the molecule is large compared to their size and the mean free path between molecular collisions is great. In liquids, the void space is much smaller, mean free paths are decreased, and diffusivities are much reduced. Thus, for an aqueous lotion on the skin, diffusion coefficients within the vehicle would be in the region of 10^{-5} to $10^{-6}cm^2sec^{-1}$. Diffusivities progressively drop as the consistency of the material increases until, for a true crystalline solid with no free volume, molecules other than small gas molecules are stopped completely. The diffusion coefficient of a drug, either in a topical vehicle or in the skin, depends on the properties of the drug and the diffusion medium and on the extent of interaction between them.

In general, during any skin permeation process, the apparent diffusion coefficient determined may reflect influences other than the intrinsic mobility of the penetrant molecules. Such influences could include changes in drug mobility through the stratum corneum arising from plasticization by vehicle or penetrant, or deviation from ideal solution behavior. Internal chemical reactions within the tissue could immobilize a fraction of the penetrant molecules. All those factors may produce concentration dependent changes. However, regardless of the mechanism which affects the magnitude of the diffusion coefficient, its value reflects the rate of penetration of a specific drug under specified condition, and diffusion coefficient is therefore a very useful parameter to know (Barry, 1983).

4.3 Partition coefficient

The single most important characteristic influencing skin penetration is distribution into the horny layer. The horny layer has for many years been identified as a non-polar membrane. Its solvent properties have therefore been mimicked by various non-polar liquids including ether, octanol and isopropyl myristate, usually expressed through an organic solvent (or "oil")/aqueous solution partition coefficient (Zatz, 1993).

The lipid/water partition coefficient denotes the ratio of the concentration of drug in two immiscible phases and is an important factor controlling the rate of transmembrane movement (Ritsche, 1988). Essentially, the stratum corneum barrier is lipophilic, with the intercellular lipid lamellae forming a conduit through which drugs must diffuse in order to reach the underlying vascular infrastructure and to ultimately access the systemic circulation. For this reason, lipophilic drugs are better accepted by the stratum corneum. A molecule must first be liberated from the formulation and partition into the uppermost stratum corneum layer, before diffusing through the entire thickness, and must then repartition into the more aqueous viable epidermis beneath. Ideally, a drug must possess both lipoidal and aqueous solubilities: if it is too hydrophilic, the molecule will be unable to transfer into the stratum corneum; if it too lipophilic, the drug will tend to remain in the stratum corneum layers (Naik, 200).

The important role that the partition coefficient may play in establishing the flux rate has been emphasized. In particular, when the membrane provide the sole or by far the major source of diffusional resistance, then the magnitude of the partition coefficient is very important. This is often the situation with percutaneous absorption, in which the resistance of the stratum corneum to the passage of the diffusant is usually the rate-limiting step in the overall absorption process. The stratum corneum to vehicle partition coefficient is crucially

important in establishing a high initial concentration in the first layer of the tissue. The relationship between partitioning behavior, chemical structure and biological activity is a pervasive theme in modern pharmaceutical literature (Barry, 1993).

Physicochemical parameters such as aqueous solubility and lipophilicity, have been shown to influence membrane flux, therapeutic activity and pharmacokinetic profiles of medicine. The use of partition coefficient in predicting the transdermal absorption of nonsteroidal anti-inflammatory drugs was found to be useful, but is advisable to include other indicative parameters (Goosen *et al.*, 1998).

A homologous series of hair dyes was selected for percutaneous absorption studies with excised human skin. The permeability constants obtained for the dyes were compared with octanol/water and skin membrane/water partition coefficient. The compounds examined were: p-phenylenediamine, o-phenylenediamine, 2-nitro-p-phenylenediamine, 2-amino-4-nitriphenol, 4-chloro-m-phenylenediamine and 4-amino-2-nitrophenol. Skin absorption of the dyes was observed when they were applied in aqueous solution. With one exception, the octanol/water partition coefficients were in the same rank order as the permeability constants. The determination of the partition of the hair dyes between water and either stratum corneum or epidermis was more complex. Preliminary stratum corneum/water partition studies results in values that were in the reverse order of the skin permeatition. When binding of the compounds to components of the membrane was saturated, the partition values more closely duplicated the rank order of permeability of the dyes. Prediction of percutaneous absorption of substances based on their partition coefficients may be confounded if these compounds are capable of binding to skin (Bronaugh & Congdon, 1984).

Figure 7 below represents the permeability data of hydrocortisone 21-esters. The best correlation of partition coefficient was found with permeability coefficient.

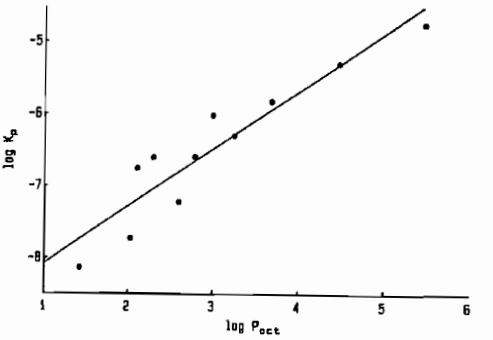

FIGURE 7: Log-log plot of permeability coefficients ($cm.s^{-1}$) versus 1-octanol-water partition coefficients for hydrocortisone 21-esters.

The octanol/buffer partition coefficients of buprenorphine and four prodrugs were determined by Stinchcomb *et al.* (1996). The results showed that, even though the flux of the prodrugs was not higher than that of parent drug, partition coefficient increase logarithmically with the increasing alkyl chain length (Table 2-2). The failure of the prodrug to deliver greater levels of buprenorphine under these circumstances is rooted in the permeation mechanism (Stinchcomb *et al.*, 1996).

TABLE 2: Partition coefficients of buprenorphine and four prodrugs.

Drug	Log K_{oct} at 25 °C
Buprenorphine	2.9
Acetyl prodrug	3.5
Propyl prodrug	3.7

Butyl prodrug	4.1
Isobutyl prodrug	4.2

It is probable that compounds which have a log K_{oct} of less than –1 will have difficulty in distributing from the vehicle into the stratum corneum and therefore only compounds with log K_{oct} > -1 can be considered as potential candidates for dermal delivery. For compounds with log K_{oct} > 2, there are potential problems in achieving steady plasma concentrations in a reasonable time span. This is due to the drug being delayed in the stratum corneum where a reservoir can be established (Guy & Hadgraft, 1989). One classic example demonstrating this is the relationship between the *in vivo* dose absorbed and the partition coefficients of a range of non-steroidal anti-inflammatory agents and salicylates. Below the optimum log K_{oct} ~ 2.5 value, the absorption rate increases with K_{oct} as a result of the larger partition coefficient providing a larger concentration gradient across the stratum corneum (Hadgraft & Wolff, 1993).

4.4 Hydrogen bonding

The most powerful determinant of diffusion across the stratum corneum is the hydrogen bonding (H-bonding) capacity of the penetrant, measured in by α (H-donor) and β (H-acceptor). The hydrogen bonding ability of a compound might be related to its relative affinities for strongly H-bonding (water) and non-H-bonding (Hexane) liquids. The strength of H-bonding of a penetrant to stratum corneum depends on its own α and β values and those of the stratum corneum. For example, in the extreme case, if the stratum corneum had a β value of zero then α of the penetrant would be irrelevant. It is likely therefore, that a partitioning solvent used to model H-bonding must have similar α and β properties to stratum corneum (Pugh *et al.*, 1996).

Anderson & Raykar (1989) suggested that the stratum corneum barrier microenvironment resembled a H-bonding organic solvent and El Tayar *et al.* (1991a) suggested that the H-bond donor potential of the solute was the dominant feature in epidermal penetration transport. In contrast, Roberts (1976) suggested that both the H-bonding donor and acceptor potential of a solute governed its transport through the epidermis.

Potts & Guy (1995) related partitioning to the drug's molecular volume (MV) and H- bond donor and acceptor activity. The H-bonding terms shows that increased solute H-bond acceptor and donor activity resulted in decreased partitioning into the organic phase due to the free energy cost associated with the disruption of H-bonds in the aqueous phase. In each case, however, a smaller decrease was seen for octanol due to the finite H-bonding ability and water solubility in this solvent. In other words, H-bonding solutes are better accommodated in octanol than in alkanes. The H-bond donor regression coefficients show that solutes with H-bond donating ability, partition least well into alkanes. Potts & Guy (1995) also documented the results which imply that the stratum corneum lipids accept H-bond better than they donate but that, like octanol, polar species can be accommodated more easily in the stratum corneum than in alkane solvents.

Solutes containing substituents which could both donate and accept H-bond (e.g $-CONH_2$, -COOH and –OH), partition similarly into stratum corneum and octanol, but less favourably into heptane. Conversely, when these substituents were replaced by groups which could only accept H-bond (e.g. $-CON(CH_3)_2$ and $-COOCH_3$), the free energies of partitioning into the stratum corneum were more similar to those into heptane than those into octanol. It follows, then that the most appropriate partitioning model for stratum corneum lipids is neither octanol-water

nor hydrocarbon-water; rather, the "correct" model depends upon the properties of the solute (Potts & Guy, 1995).

Pugh *et al.* (1996) examined the effect of specific H-bonding groups on diffusion across the stratum corneum, estimated the H-bonding potential of the stratum corneum and examined how far the technique is applicable to polyfunctional compounds. Calculated diffusion coefficient was obtained using equation 3:

$$\log (D/h) = -1.32 - 1.30\alpha - 2.57\beta \qquad \text{(Equation 3)}$$

and regressed against the number (1 or 0) of each functional group responsible for H-bonding.

$$\log (D/h) = -1.36 - 1.67\text{acid} - 1.41\text{alcohol} - 1.17\text{phenol} - 0.986\text{carbonyl} - 0.759\text{ether} - 0.0502C^* \qquad \text{(Equation 4)}$$

Where "log (D/h) is the diffusion across the stratum corneum, "acid" is the interger number of acid groups present and C* is the number of carbon atoms not involved in H-binding. Table 3 present the α and β of the functional groups.

TABLE 3: Hydrogen bonding values of different functional groups (Pugh *et al.*, 1996).

Group	α	β
Alcohols	0.37	0.48
Phenols	0.57	0.32
Acids	0.60	0.45
Ether	0.00	0.45
Ketone	0.00	0.51
C*	0.00	0.00

The stratum corneum lipids was calculated to have 14.33 total α effect and the β effect as 21.54 and reported that the maximum rate of diffusion of an infinitely small, non-bonding molecule is about 0.03 cm/h (Pugh *et al.*, 1996).

In a study by Beall *et al.* (1994), the solubility of the 1-akyloxycarbonyl series of 5-flourouracil prodrugs showed that removing the amide-like NH group from the promoiety and replacing it with an oxygen group significantly increases the water solubilities of at least the first four members of the series. The change also improved their lipid solubilties as well.

4.5 Melting point

The melting point of substances reflects their relative hydrophobia associated with a low level of crystalline interactions. Drug crystallinity, or melting point, influences permeability and was found to be inversely proportional to lipophilicity (log K_{oct}). The melting point of a substance is often considered to be an indicative of the maximum flux attainable through the skin. The lower the melting point, the greater is the drugs ability to permeate the skin. It is assumed that there should be an exponential increase in dermal flux with a decreasing melting point (Calpena *et al.*, 1994, Cleary, 1993 and Guy & Hadgraft, 1989).

Calpena *et al.* (1994) conducted a study to determine the permeation parameters (transdermal permeability rate (k_p), lag time and flux) as a measure of the intrinsic permeability of various anti-emetic drugs across the skin. The k_p varied inversely with melting point, compounds with lower melting point had higher k_p values (Figure 2-8).

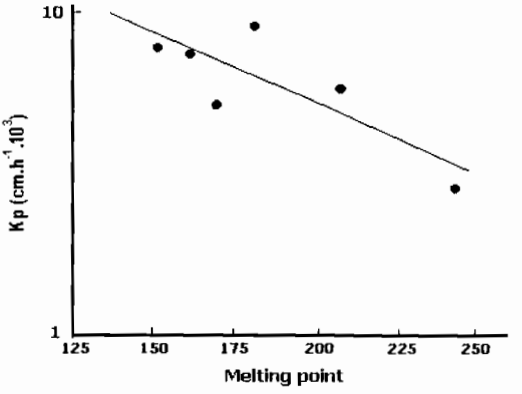

FIGURE 8: Linear relationship between log k_p values and melting point (mp) for anti-emetic drugs assayed (Calpena *et al.*, 1994).

Linear correlation was found between logarithm of k_p and the melting point as expressed by equation 5.

$$\text{Log } k_p = 1.6018 - 0.004461mp \qquad \text{(Equation 5)}$$

$(r = 0.8120; p > 0.05)$

Kerr and colleagues (1998) determined the melting points and other physicochemical properties (i.e lipid solubility, partition coefficient (K_{oct})) of alkylcarbonylmethyl prodrugs of theophylline. The data presented in Table 2-4 reflects the correlation between melting point, lipid solubility and partition coefficient. Lipid solubility and partition coefficient increase with decrease in melting point. The first several members of a series are usually the members that give the greatest increase in delivery of the parent drug.

TABLE 4: Melting point (mp), lipid solubility (S_{LMP}) and partition coeffients for 1-alkylcarbonyloxymethyl prodrugs of theophilline (Kerr *et al.*, 1998)

Alkyl =	Mp (°C)	S_{IPM} (±SD) (µmol/ml)	K_{oct} ± SD
Th	270 – 274	0.34	0
CH_3	163.5 – 165	2.75 (0.099)	0.141 (0.006)
C_2H_5	146 – 147	2.93 (0.11)	0.634 (0.05)
C_3H_7	104 –105	25.4 (0.32)	2.41 (0.27)
C_4H_9	86 – 87	44.0 (1.5)	8.42 (0.18)
C_5H_{11}	58 – 60	77.8 (0.45)	28.0 (2.5)

4.6 Ionisation

The pH partition theory is well documented for general absorption of ionisable drugs across the gastro-intestinal tract, but it is less well described in the dermal and transdermal delivery of drugs. This is perhaps surprising given the number of medicines that are delivered to the skin and which would be ionised over the normal physiological pH range of the dermal tissues (4-7.4). It is generally accepted that, where possible, the free acid or free base should be used, however perhaps this premise should be questioned (Hadgraft & Valenta, 2000). Lund (1990) also documented that, where a drug molecule is capable of dissociating into ions, equilibrium exists between the ionized and unionized species. However is only the unionized form that is appreciably absorbed. Because the proportion of ionized and unionized forms of the weak acids and bases varies with the hydrogen ion concentration, pH changes can alter markedly their rate of absorption.

A strong acid or strong base will exist in the ionized form at all pH values and will be poorly absorbed through membranes. For weak acids and bases the proportion of unionized absorbable species and ionized non-absorbable species can be calculated at any pH if the dissociation constant or (ionization constant, K_a) for the acid or base is known. The dissociation constant of a weak acid (HA)

ionizing to give hydrogen ions (H^+) and ions of the conjugate base (A^-) is defined by:

$$K_a = \frac{[H^+][A^-]}{[HA]} \qquad \text{(Equation 6)}$$

where $[H^+]$, $[A^-]$ and [HA] are the concentrations of the hydrogen ions, conjugate base and unionized acid respectively. The pK_a value for an acid is the common logarithm of the reciprocal of the dissociation constant, and is a measure of acid strength. A pK_a value below 2.5 indicates a strong acid. Weak acids have pK_a value in the range 2.5 to 8 and very weak acids a pK_a value greater than 8. The relative proportions of ionized and unionized species can be calculated from the Henderson-Hasselbalch equation:

$$\log_{10}\frac{[A^-]}{[HA]} = pH - pK_a \qquad \text{(Equation 7)}$$

Ionization of weak base (B) may be represented as producing hydroxyl ions (OH) and ions of the conjugate acid (BH^+) (Lund, 1994):

$$K_b = \frac{[BH^+][OH^-]}{[B]} \qquad \text{(Equation 8)}$$

A high pK_a value indicates a strong base and equation 9 predicts that the proportion of ionized species is increased by a decrease in pH.

$$\log_{10}\frac{[BH^+]}{[B]} = pK_a - PH \qquad \text{(Equation 9)}$$

According to Hadgraft & Valenta (2000), the transport properties of a permeant can be described by the permeabilities of the ionized and unionized species and the respective concentrations k_{ion}, k_{punion}, c_{ion} and c_{union} respectively.

$$J_{tot} = k_{punion} * c_{union} + k_{pion} * c_{ion} \qquad \text{(Equation 10)}$$

(J_{tot}) = total flux of the permeant

For any given pH, pK_a and total applied concentration, it is therefore possible to calculate the amounts of c_{ion} and c_{union}.

If passive diffusion is the predominant mechanism for percutaneous penetration of methotrexate, then changes in vehicle pH would be expected to influence the *in vivo* percutaneous absorption of methotrexate through human cadaver skin, since transport by passive diffusion is generally maximized when the drug is present in the unionized form. Table 5 presents the effect of pH on *in vitro* percutaneous penetration of methotrexate (Vaidyanathan, 1985).

TABLE 5: Effect of pH on *in vitro* percutaneous penetration of methotrexate (Vaidayanathan, 1985).

pH	Steady-state penetration rate ($ug.cm^{-2}h^{-1}$)
1.98	0.1588
2.98	0.1995
3.87	0.4064
4.12	0.3182
5.29	1.6687
6.34	2.5819

Smith (1990) documented that the transdermal absorption of scopolamine was shown to be substantially higher at pHs above the pK_a of the weak base, in general higher fluxes will be obtained by maintaining the pH such that the penetrant is unionized. It should be noted that nonphysiological pHs may also change properties of the skin, that could affect solubility, partitioning or binding, resulting in changes in dermal penetration. Swabrick *et al.* (1984) found that the

permeability coefficient of the unionized chromone-2-carboxylic acids were approximately 10 000 larger than those of the corresponding ionized species.

4.7 Molecular size

It is well documented that the molecular size of a substance directly affects its diffusion across simple or complex membranes. The diffusion of molecules through liquids is inversely proportional to the molecular weight of the molecules or to the square or cube root thereof. This phenomenon may also be expected in the case of diffusion across the skin (Calpena *et al.*, 1994). Considering that the horny layer is a compact membrane and that diffusing molecules follow a tortuous path through it, it might seem obvious that the diffusion coefficient would be inversely related to molecular weight (MW) or some measure of molecular size (Zats, 1993). Diffusivity is a kinetic term, and is a rough measure of the ease with which a molecule can move about within a medium (in this case, the skin). The larger the molecule, the more difficult it is to move about, and the lower the diffusivity (Smith, 1993).

Lund (1994) documented that, molecules of small sizes in high concentration tend to penetrate more readily than large molecules. However, for a range of chemically equivalent molecules with similar molecular weight, there is little correlation between their size and absorption potential.

Several authors used the following equation to relate diffusion (D) to size:

$$D = D_o (MW)^b \qquad \text{(Equation 11)}$$

D_o is the diffusion coefficient and b refers to the mass selectivity coefficient. For diffusion across membranes, apparent values of b from –3 to –5 indicate a strong dependence of diffusion on molecular weight (Pugh *et al.*, 1996). Anderson and

Raykar (1989) using cresol and hydrocortisone esters (N = 16), used other penetration parameter such as k_p rather than D (Equation 12, where b = -4.6)

$$k_p = \text{constant}.(K_{oct})^a.\ (MW)^b \qquad \text{(Equation 12)}$$

In the study by Calpena *et al.* (1994), no relation was observed between the molecular weight and the transdermal permeability rate constant (k_p) of the antiemetics studied (Table 6). Alizapride, bromopride and metoclopramide on the one hand and clebopride, domperidone and metopimazine on the other have similar MWs but show clear differences in their k_p values. Other physicochemical characteristics may be more directly involved in dermal permeability, whereas MW may be a secondary factor when there are only small differences in the MWs.

TABLE 6: Molecular weights, transdermal permeability rate constants (k_p) and estimated fluxes (J) (Calpena *et al.*, 1994).

Drug	k_p (cm/h) x 10^3	J (mg/cm^{-2}/h) x 10^2
Alizapride	5.7 ± 3.2	2.82 ± 1.58
Bromopride	7.8 ± 2.1	3.89 ± 1.05
Clebopride	7.4 ± 4.2	3.71 ± 2.09
Domperidone	2.8 ± 0.9	1.40 ± 0.44
Metoclopramide	9.1 ± 2.5	4.54 ± 1.27
Metopimazine	5.1 ± 1.4	2.53 ± 0.78
Scopolamine	4.1 ± 1.8	2.03 ± 0.90

5 The influence of alkyl chain length on percutaneous absorption

Molecular modification of active substance can have marked effects on their activity. Changes in functional groups that alter the solubility and the partition

coefficient of the substance between the vehicle and the skin barrier may retard or enhance skin penetration (Lund, 1994). Improvement in delivery of a drug frequently requires the design of transient derivatives of the drug which are called prodrugs. The design of prodrugs that exhibit the desired hydrophilic/lipophilic balance in their solubility which is necessary for the efficient dermal or transdermal of their parent drug, requires precise knowledge of the relative aqueous and lipid solubilities of the members of the proposed series of prodrugs (Beall, 1993a). An understanding of the manner in which these physicochemical properties (aqueous and lipid solubilities, partition coefficient and others) change within a homologous series i.e incremental addition of methylene units, can be of use in choosing a derivative having optimum properties (Yalkowsky *et al.*, 1972).

For a homologous series of chemicals, lipid/water partition coefficient increases exponentially with increasing chain length. Thus for a membrane of fixed or normalized thickness, the permeability coefficient through a lipid pathway will directly reflect partitioning and will follow:

$$P_n = P_{(n=10)}\, 10^{\pi n} \qquad \text{(Equation 13)}$$

In this equation, n is the alkyl chain length, $P_{(n=10)}$ is an intercept value equating to the homologue with no alkyl chain length, and π is a positive constant related to the free energy of partitioning of a methylene unit. This relationship holds as long as the rate-determining step in crossing the membrane is passage through a lipid region; the equation indicates that, for a pure lipid membrane, a plot of the logarithm of the permeability coefficient versus the alkyl chain length of the permeant will be a straight line with an intercept at $P_{9n=100}$ and a slope equal to π (Walters, 1990).

According to Yalkowsky & Flynn (1973), equation 14 is a useful relationship which allows chain length (n) to be used in lieu of partition coefficients (log K_n) in theoretical analysis.

$$\text{Log}K_n = \log K_o + \Pi_n \qquad \text{(Equation 14)}$$

Depending on the organic phase chosen, the value of Π, the slope of the $\log K_n$ versus *n* plot, can be as small or smaller than 0.3 and as large as 0.7. Values of 0.3 to 0.5 are typical for biological membranes. At the lower end of the range it takes an addition of three methylene units to the alkyl chain length to produce a 10-fold increase in partition coefficient. Two methylene units produce this effect when the Π value hovers around 0.5.

The permeation of simple hydrophobic membranes by alkyl homologue applied to the membrane aqueous solution often evidences a dominating influence of o/w partitioning on the permeability coefficient through the short to middle chain length of the series (Flynn, 1989). This is illustrated in Figure 9, in which permeability coefficient profiles for three homologous series permeating silicone rubber membranes are described (Flynn & Yalkowsky, 1972).

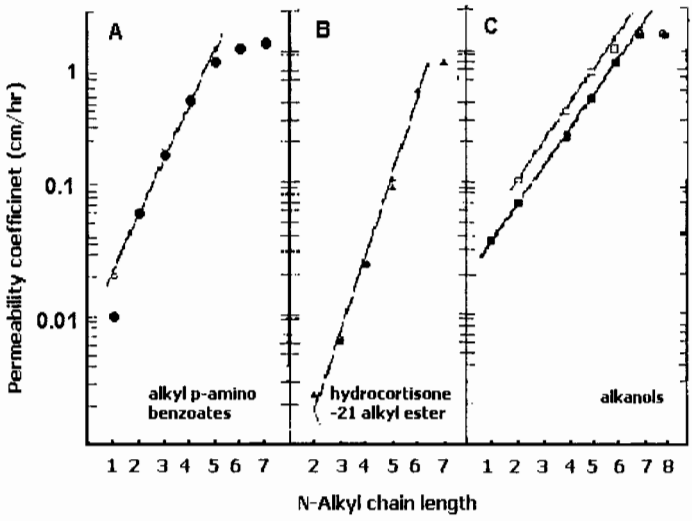

FIGURE 9: Series of plots of 37 °C permeability coefficients as a function of alkyl chain length. (A) Data for the alkyl-*p*-amino benzoates, (B) the hydrocortisone-21-alkyl ester permeability coefficients and (C) data for the homologous *n*-alkanols through 74μm (□) and 100μm (■) homemade silicone rubber membranes (Flynn & Yalkowsky, 1972).

It is seen that $\log K_{oct}$ for short-chain membrane of each of these very different homologous series rises sharply and linearly with increased length of the alkyl chain. It will also be noticed that for each series the profile levels out at some long-chain length. Partitioning into the membrane follows the $\log K_n$ versus n homologous relationship expressed in equation 14. At the shorter chain length the o/w partition coefficient is very small and consequently the membrane resistance is high enough to totally control the rate of the permeation process. However, as the chain is lengthened, the resistance of the membrane is exponentially decreasing owing to its reciprocal dependency on the o/w partition

coefficient. The summed resistance of the boundary layers at the same time remains unchanged or even increases gradually because of the effect of increasing molecular size on diffusivity. Consequently, a point is reached at which the low, but unchanging, resistance of the boundary layers assumes rate-controlling proportions (Flynn, 1989).

Yalkowsky *et al.* (1972) investigated the importance of alkyl chain length on physicochemical properties (i.e., melting points, solubilities and partition coefficients) of an organic homologous series of alkyl *p*-aminobenzoates. The melting points of the alkyl *p*-aminobenzoic acid esters determined by DSC are shown in Figure 10. As chain length is increased, the melting point decreases almost linearly to the butyl ester and then increases gradually and irregularly. The solubilities of each ester studied in water, silicone oil and hexane provide estimates of the partition coefficients of each homolog between the immiscible phases. The logarithm of the partition coefficient is linearly dependent on chain length. Figure 11 shows this linearity and the absence of an inflection point at four carbons for both the silicone oil-water and the hexane-water partition coefficients.

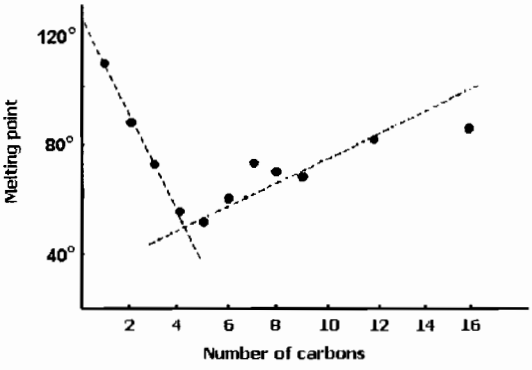

FIGURE 10: Melting points of alkyl *p*-aminobenzoates. (Yalkowsky *et al.*, 1972).

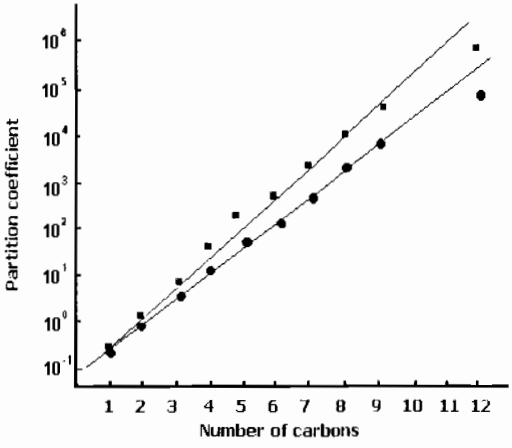

FIGURE 11: Partition coefficients of alkyl *p*-aminobenzoates. •, silicone oil-water; and ■, hexane-water. (Yalkowsky *et al.*, 1972).

The curve of melting points (Figure 10) shows a sharp change in slope at the butyl derivative. This is because melting points of crystalline materials are heavily dependent upon crystal energies. It is proposed that the nonlinearity of the curve is due to a change in crystal structure with chain length. The crystal structure of the lower homologs is probably determined primarily by the aromatic ring and the dipolar nature of the moiety. If the chain is increased beyond four carbons, the linear aliphatic chains begin to exert a dominating effect. This is also true for the solubilties. Partition coefficient is a property of the solute and therefore is not dependent on crystal structure, is only dependent upon the interactions occurring in solution (Yalkowsky *et al.*, 1972).

Flynn & Yalkowsky (1972) on their study of the effect of alkyl chain length on the flux across a synthetic membrane found that a plot of the logarithm of steady-state flux from saturated solution against chain length gave a parabolic curve. The maximum flux is attained between C-3 and C-4. For chain length increasing beyond C-4, the flux decreased due to diminished aqueous solubility. These results indicate that the mechanism of diffusion passes from regulation by the membrane to being governed by the diffusion layer at about C-4. Sasaki *et al.* (1990) obtained similar results, whereby the butyl derivative (C-4) showed the highest flux. The flux decreased with greater alkyl chain length of the derivative.

6 Conclusion

Skin permeation and uptake measurements are useful in product development and toxicologic evaluation. The target site of action and intended use of a product determine the type of absorption behaviour that is most desirable. For most compounds, the horny layer (stratum corneum), the outermost skin section consisting of a compressed amalgam of dead cells separated by oriental layers

of neutral lipids, represents the principal barrier to transport. This makes possible the use of excised skin in *in vitro* diffusion experiments. Shunt diffusion via follicles and glands may contribute significantly to the absorption of many drugs (Zats, 1993).

The major advantage claimed for percutaneous absorption is that it avoids the vagaries of the gastrointestinal milieu and does not shunt the drug directly through the liver, thereby avoiding the "first-pass" effect. The major disadvantages for percutaneous absorption are related to the barrier properties of the skin.

The major route of penetration through the stratum corneum is via the lipid-rich intercellular channels. Thus, the first physicochemical constant that can be identified as being significant is the lipid/water partition coefficient of the drug. Another parameter that should be taken into account is the solubility of the drug in the skin lipids. Ideally it should be possible to predict the rate and extent of percutaneous absorption from the knowledge of the simple physicochemical properties of the drug.

As the full metabolic potential of the skin is gradually being unravelled along with the physicochemical processes involved in the dermal diffusion process, it can be anticipated that more prodrugs will be designed for dermal delivery to optimize the bioavailability of each drug delivered via the percutaneous route, for either local or systemic action (Chan & Li Wa Po, 1989).

It is thus clear that the skin is an excellent barrier, but can in some instances be used as target in order to deliver drugs through and into the skin.

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