International Journal of Pharmaceutics 373 (2009) 1–3

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Rapid communication

Transepidermal water loss and skin site: A hypothesis

Jonathan Hadgraft*, Majella E. Lane

Department of Pharmaceutics, The School of Pharmacy, 29-39 Brunswick Square, London, WC1N 1AX, United Kingdom

ARTICLE INFO

Article history:
Received 4 February 2009
Accepted 9 February 2009
Available online 21 February 2009

Keywords:
Skin
Transepidermal water loss
Corneocyte size
Protease activity
Cell layers

ABSTRACT

The skin has a unique barrier to the ingress of hazardous materials and the egress of water. The barrier properties of the skin reside in the outer 15 μm, the stratum corneum, which has often been regarded as rather inert or even dead. The excellent barrier properties of this thin layer result from its structure which comprises of pentagonal or hexagonal corneocytes embedded in a lipid matrix. Corneocyte turnover and epidermal proliferation is controlled by desquamatory proteases and protease inhibitors in the epidermis. Disorders in barrier function and disruption of barrier homeostasis have been associated with changes in the expression patterns of epidermal serine proteases and variations in serine protease activity have also been identified at different body sites. The major route of permeation is around the corneocytes, therefore, the larger the corneocytes the longer the route for the permeation. Corneocyte size is dependent on the site on the body and this can be directly related to the permeability. For example, the face has thinner skin and the corneocyte size is smaller than the arm. This results in a shorter path for a drug to penetrate. Transepidermal water loss (TEWL) is a measure of the amount of water from within the skin to the external atmosphere. Rougier et al. showed that variations in corneocyte size at different anatomical sites were reflected in TEWL at these sites. The path length at different body sites was calculated using a simple geometric equation and a direct reciprocal relationship between the path length and TEWL was identified. A linear trend between cell size and cell layers at different sites is also evident in the data. Since higher protease activity should result in smaller corneocyte sizes and fewer cell layers, this in turn may be related to reported variations in enzyme activity at these sites.

The skin has evolved over many millennia to be a unique barrier to the ingress of xenobiotics and the egress of water. The barrier properties of the skin reside in the outer 15 μm, the stratum corneum which has always been regarded as rather inert or even dead. Even though the layer is very thin, it has remarkable barrier properties which result from its structure which resembles a brick wall (Michaels et al., 1975) which is reinforced with steel rivets (Cork et al., 2006) (Fig. 1). Breakdown of this skin barrier is the first event in the development of atopic eczema, which may lead on to food allergy, asthma and allergic rhinitis: the so called atopic march.

The bricks are the dense corneocyte cells which are typically long thin pentagonal or hexagonal plates. The predominant route of penetration of xenobiotics is through the 'mortar' (Albery and Hadgraft, 1979) which is composed of a complex mixture of lipids which are structured into rigid bilayer arrays. Water also diffuses along this tortuous route (Potts and Francoeur, 1991). Unlike other biological membranes there are no phospholipids, these have been replaced by a group of ceramides, free fatty acid, cholesterol and cholesterol esters (Wertz, 1992).

The diffusional barrier results from both the properties of the lipids and the pathlength for diffusion which depends on the number of layers of corneocytes, their size and their cohesion. The larger the corneocytes the longer the route and the lower the permeation. The size is dependent on the site of the body and this can be directly related to the permeability (Rougier et al., 1988). For example, the face has thinner skin and the corneocyte size is smaller. This results in a shorter path for a drug to penetrate to the viable epidermis.

The data presented in Rougier et al. (1988) can be combined with information about the variation in the number of cell layers (n) at various skin sites (Ya-Xian et al., 1999). If the corneocytes are assumed to be simple squares that overlap one another it is possible to calculate the pathlength for diffusion by simple geometry. Rougier et al. (1988) provide the corneocyte surface area (A), the average thickness of a corneocyte is 1 μm and, therefore, the pathlength is $(n + \sqrt{A(n-1)/2}$. The tortuosity factor (diffusional pathlength/stratum corneum thickness can also be estimated from this approach and for the forearm, an area of average skin permeability, the values are approximately 15. This compares very well with that determined by Talreja et al. (2001) using confocal microscopy of 13.

In the publication of Rougier et al. (1988), data are presented relating transepidermal water loss (TEWL (as an indicator of skin

* Corresponding author. Tel.: +44 2077535821; fax: +44 870 1659275.
E-mail address: jonathan.hadgraft@btinternet.com (J. Hadgraft).

0378-5173/$ – see front matter © 2009 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2009.02.007

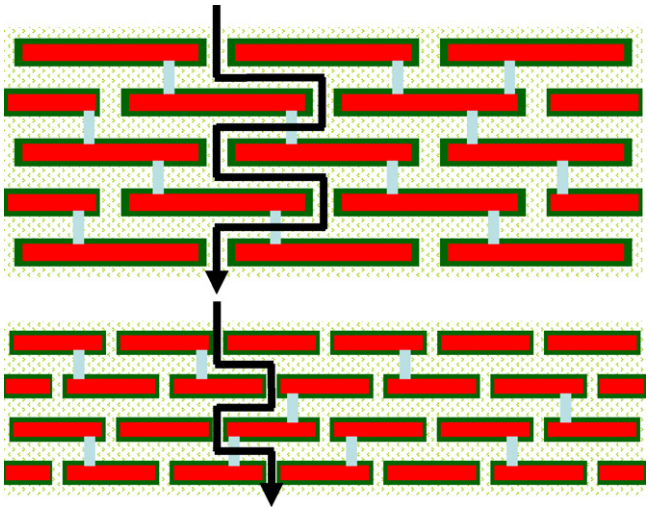

Fig. 1. The upper diagram represents the bricks and mortar structure for the forearm (larger corneocytes and more layers) and the lower one for the face. The grey 'rivets' represent the corneodesmosomes.

permeability)) with corneocyte size. These have been replotted in Fig. 2.

The TEWL, however, should be linearly related to the reciprocal of the diffusional pathlength (Fick's First law of diffusion as shown in Eq. (1)). The pathlength, given the assumptions above, can be calculated using Eq. (2).

$$\text{TEWL} \alpha \text{D} \frac{K_{\text{water}}}{\text{pathlength}} \quad (1)$$

$$\text{Pathlength} = \left(\frac{n + \sqrt{\text{A}(n-1)}}{2} \right) \quad (2)$$

where K_{water} is the partition coefficient of water from the viable tissue into the stratum corneum lipids and D is the diffusion coefficient of water through these lipids.

Fig. 3 shows the data reported by Rougier et al. (1988) and replotted in this way. There is a direct relationship between the reciprocal of the pathlength and skin permeability as assessed by TEWL measurements. It is interesting to note that as the pathlength becomes infinitely long TEWL tends to become zero which is intuitively correct.

In other words as cell size gets bigger and the number of cell layers increase the skin barrier function becomes larger. This has a major impact on drug penetration. On the face the corneocyte size is smaller, there are fewer layers and permeation is more rapid, hence the caution advised in the use of topical corticosteroids on facial areas.

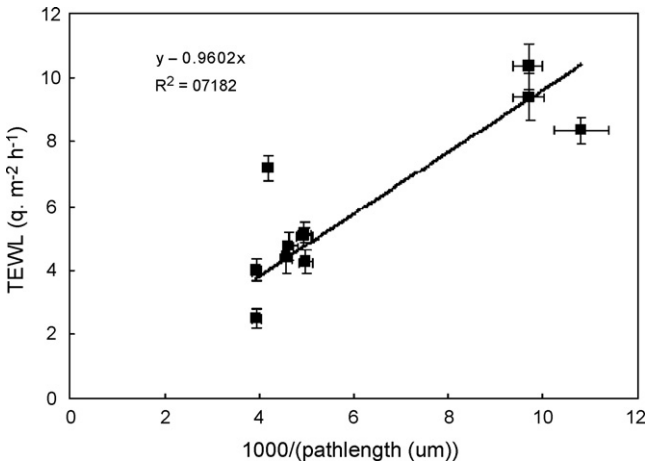

Fig. 3. The relationship between TEWL and the reciprocal of the estimated pathlength for diffusion.

The skin is a dynamic barrier with a normal turnover time for the stratum corneum of 14 days. The sloughing off process of the cells involves the breakdown of the 'rivets' (the corneodesmosomes) that hold the cells together by proteases such as stratum corneum chymotryptic enzyme (SCCE). It is proposed that where there is more protease activity the cells do not mature so long, they are smaller and there are fewer layers. This can be seen in Fig. 4 in which corneocyte size has been related to the number of cell layers. While it is appreciated that the number of data points are small a trend is observed which requires more detailed investigation.

A comparison has been made between the forearm and cheek levels of SCCE; there is 3-fold more in the cheek (Voegeli et al., 2007). This is in line with the smaller corneocytes, the thinner and more permeable skin in the facial area.

In conclusion it is important to recognise the variation in skin permeability with body site and disease state. The above analysis shows an explanation for the variation with body site and suggests that the predominant reason for this is the corneocyte size and number of cell layers. There is an indication that this could be related to enzyme activity in the stratum corneum which

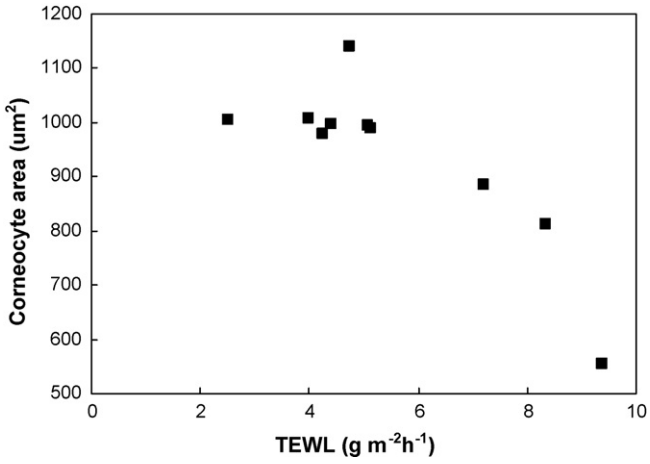

Fig. 2. The relationship between TEWL and corneocyte size, data replotted from Rougier et al.

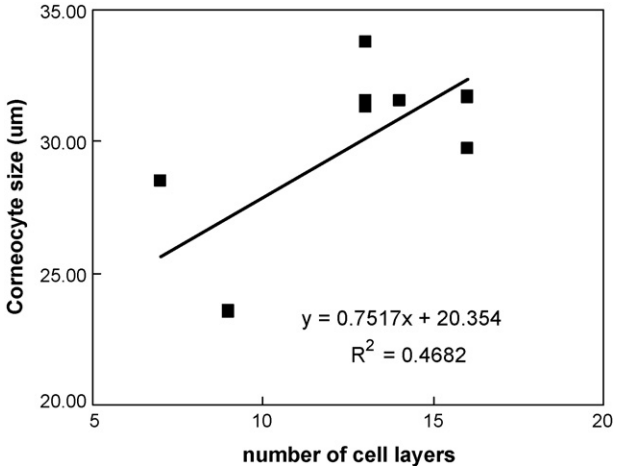

Fig. 4. The relationship between cell size and number of layers, data from Rougier and Ya-Xian.

influences corneocyte maturity hence size and number of layers. If this can be substantiated it should have significant impact in understanding permeability changes in diseased states such as eczema and psoriasis in which the homeostasis of the enzymes (such as SCCE) are perturbed. These are important issues that are currently under more detailed investigation. They will help in the delivery of topical actives and aid formulation design.

References

Albery, W.J., Hadgraft, J., 1979. Percutaneous absorption: in vivo experiments. J. Pharm. Pharmacol. 31, 140–147.

Cork, M.J., Robinson, D.A., Vasilopoulos, Y., Ferguson, A., Moustafa, M., MacGowan, A., Duff, G.W., Ward, S.J., 2006. New perspectives on epidermal barrier dysfunction in atopic dermatitis: gene-environment interactions. Curr. Rev. Allergy Clin. Immunol. 118, 3–21.

Michaels, A.S., Chandrasekaran, S.K., Shaw, J.E., 1975. Drug permeation through human skin: theory and in vitro experimental measurement. Am. Inst. Chem. Eng. J. 21, 985–996.

Potts, R.O., Francoeur, M.L., 1991. The influence of stratum corneum morphology on water permeability. J. Invest. Derm. 96, 495–499.

Rougier, A., Lotte, C., Corcuff, P., Maibach, H.I., 1988. Relationship between skin permeability and corneocyte size according to anatomic site, age and sex in man. J. Soc. Cosmet. Chem. 39, 15–26.

Talreja, P.S., Kleene, N.K., Pickens, W.L., Wang, T.F., Kasting, G.B., 2001. Visualization of the lipid barrier and measurement of lipid pathlength in human stratum corneum. AAPS PharmSci. 3, 13, article.

Voegeli, R., Rawlings, A.V., Doppler, S., Heiland, J., Schreier, T., 2007. Profiling of serine protease activities in human stratum corneum tryptase-like enzyme. Int. J. Cosmet. Sci. 29, 191–200.

Wertz, P.W., 1992. Epidermal lipids. Semin. Dermatol. 11, 106–113.

Ya-Xian, Z., Suetake, T., Tagami, H., 1999. Number of cell layers of the stratum corneum in normal skin – relationship to the anatomical location on the body, age, sex and physical parameters. Arch. Dermatol. Res. 291, 555–559.