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Viewpoint

The 500 Dalton rule for the skin penetration of chemical compounds and drugs

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Abstract: Human skin has unique properties of which functioning as a physicochemical barrier is one of the most apparent. The human integument is able to resist the penetration of many molecules. However, especially smaller molecules can surpass transcutaneously. They are able to go by the corneal layer, which is thought to form the main deterrent. We argue that the molecular weight (MW) of a compound must be under 500 Dalton to allow skin absorption. Larger molecules cannot pass the corneal layer. Arguments for this "500 Dalton rule" are; 1) virtually all common contact allergens are under 500 Dalton, larger molecules are not known as contact sensitizers. They cannot penetrate and thus cannot act as allergens in man; 2) the most commonly used pharmacological agents applied in topical dermatotherapy are all under 500 Dalton; 3) all known topical drugs used in transdermal drug-delivery systems are under 500 Dalton. In addition, clinical experience with topical agents such as cyclosporine, tacrolimus and ascomycins gives further arguments for the reality of the 500 Dalton rule. For pharmaceutical development purposes, it seems logical to restrict the development of new innovative compounds to a MW of under 500 Dalton, when topical dermatological therapy or percutaneous systemic therapy or vaccination is the objective.

Jan D. Bos and Marcus M. H. M. Meinardi

Department of Dermatology, Academic Medical Center, University of Amsterdam, The Netherlands

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Jan D. Bos, Department of Dermatology A0-235, Academic Medical Center, University of Amsterdam, P.O. Box 22700, 1100 DE Amsterdam, The Netherlands
Tel.: +31 20 566 2587. Fax: +31 20 696 0076
e-mail: j.d.bos@amc.uva.nl

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Introduction

Human skin has many functions and its most apparent is that of a defense organ, both physical and biological (1). Penetration from outside into the body of any compound is primarily prevented by the corneal layer of the epidermis. This outer layer is just a few micrometers thick, but effectively forms a barrier that is indeed preserving life. Although absorption is not only dependent on penetration, but also on other variables such as skin metabolism, insufficient release from the carrier, partitioning in an unwanted reservoir, without penetration nothing happens. It is important to realize that the human skin has unique properties in this respect and that penetration studies performed in animal models are of limited use for our understanding of the human skin barrier.

Essentially, the corneal layer consists of apoptotic keratinocytes that have transformed themselves into keratin-rich, lipoprotein-containing envelopes and lipid bilayers with hydrophilic regions in between. Most medicaments will pass the epidermal barrier through the intercellular route. As a consequence of its hydrophobic nature, the stratum corneum barrier will allow the penetration of lipid soluble molecules more readily than water-soluble compounds. Strong lipophilic compounds will however be hampered by the hydrophilic regions in the bilayer. Water-soluble molecules may penetrate through an alternative way, the openings of sweat glands and hair follicles. The total surface of these openings amounts to 0.1% of the total skin surface area, making it probably not significant.

The only way to circumvent the properties of the corneal layer is by disrupting it, for example with ultrasound, a method also known as phonopheresis (2), or with high-voltage electrical pulsing, also known as electroporation (3, 4). Alternative methods such as stripping the corneal layer using adhesive tape have also been advocated but are not reliable. The use of skin penetration enhancers such as dimethylsulphoxide or carriers such as liposomes have never been confirmed to make a difference. Iontopheresis (5) using low-voltage has been developed for increasing the flux of particular