Research Techniques Made Simple: Drug Delivery Techniques, Part 1: Concepts in Transepidermal Penetration and Absorption

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INTRODUCTION

In dermatology, topical therapies are usually the first line and mainstay of treatment for the majority of skin conditions. Most topical preparations are available in a variety of potencies and delivery systems. Practitioners must carefully choose from this vast array based on the potency required, location of intended use, product elegance, and likelihood of patient compliance. Unfortunately, information concerning which preparation is truly best, regarding actual penetration and delivery to the site of action, is not readily available. In general, many practitioners believe that ointments and foams enhance penetration when compared to creams, gels, and powders. However, this is not always the case. Aside from vehicles, there are a variety of chemical and physical enhancement techniques that influence topical penetration. As physician-scientists, dermatologists should be aware of the basic mechanisms involved in topical absorption and should be able to assess whether a preparation is likely to exert its desired effect. In this article, we explore the inherent properties of the epidermis and the physiology of passive diffusion and aim to clarify the definition of the terms "absorption" and "penetration."

KEY POINTS

- The terms "absorption" and "penetration" are often used interchangeably, which is incorrect.
- "Absorption," or "accumulation," refers to the amount of substance that builds up in the skin over a certain period of time whereas "penetration" is the amount of a substance that crosses the skin per unit area per unit time.
- The stratum corneum is the greatest barrier against drug penetration.
- The extracellular lipid composition of the epidermis plays a large role in barrier function.
- There are numerous techniques, both passive and active, to enhance drug penetration through the skin.

ACCUMULATION VERSUS PENETRATION

The terms "absorption," which is the accumulation of drug in the skin, and "penetration," which is a measure of flux/transport across the skin, are often incorrectly used interchangeably. Penetration is quantifiable as the amount of substance that crosses the skin per unit area per unit time. By contrast, "absorption," or "accumulation," refers to the amount of a substance that builds up in the skin over a certain time period. The accumulated substance may remain in the skin or leave the skin to enter the systemic circulation. Whether the substance exerts a biological effect, is inert, is metabolized (and at what rate), and/or is soluble can impact the substance's concentration in the skin at any given time, making the results difficult to compare and reproduce.

There are two general routes through which topically applied preparations can enter the skin: transepidermal (via the stratum corneum) and transappendageal (via appendages such as eccrine ducts and hair follicles). Transepidermal penetration can be either transcellular (through the corneocytes and the lipid lamella) or intercellular (through a complex pathway along the lipid lamella). Generally, it is believed that the penetration of topical drugs occurs primarily through the intercellular route, given the hydrophobic nature of the extracellular space. Although it has traditionally been thought that the transcellular and transappendageal routes contribute only slightly to the overall drug transport, the former is important for small hydrophobic molecules and the latter may in fact be underestimated in certain cases. Transappendageal transport of the follicular type has become a focus of research in the past decade because hair follicles represent an effective reservoir and contain target sites such as stem cells and dendritic cells. The reservoir effect of follicles is profound, measuring up to 10 times larger than that of the surrounding skin (Shah *et al.*, 2014). However, there are two major issues with the follicular pathway. The first is the fact that although some substances can pass deep into hair follicles, none has been able to pass transfollicularly into the surrounding skin or penetrate into the circulation. The second is the lack of a proper skin model other than intact human skin for researching transport through the transfollicular pathway.

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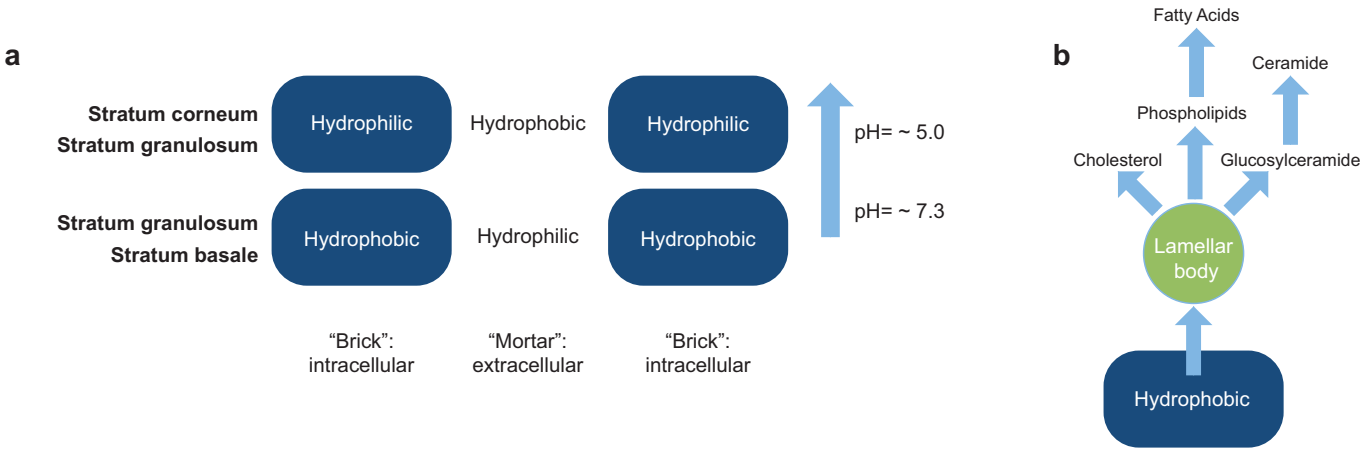

Figure 1. Basic structure of the stratum corneum. (a) "Bricks-and-mortar" model of the epidermis. The extracellular space of the stratum granulosum and stratum corneum exhibits hydrophobic properties due to its lipid-rich composition. This is in contrast to the layers below the stratum granulosum, which exhibit a hydrophilic environment due to the lipid-poor, desmosome-rich composition. pH = ~7.3 in stratum granulosum; pH = ~5.0 in the mid–stratum corneum. (b) Formation of lipid-rich extracellular space. Expulsion of lamellar bodies and conversion of lipids into final end products.

One approach to solving the penetration problem is the use of triggered release mechanisms. This allows the drug to be released independently after it has been delivered deep into the hair follicle. The drug can then pass through the hair follicle and into the surrounding skin. Currently, a number of these release triggers are under investigation and include radiofrequency, ultrasound, light, enzymatic reactions, and pH manipulation (Shah *et al.*, 2014).

BARRIER PROPERTIES OF THE SKIN

The stratum corneum of the stratified epidermis functions as the single greatest barrier against drug penetration (Bouwstra *et al.*, 2001; Jain, 2008). A major component of this barrier is extracellular lipids, which are extruded into the extracellular space as cells transition from the granular layer to the stratum corneum. In conjunction with this lipid-rich extracellular space, limited desquamation of corneocytes provides a homeostatic layer of cells that protects the underlying epidermis. Together, this arrangement of corneocytes in the stratum corneum and the formation of a lipid-rich extracellular space has been coined the "bricks-and-mortar" model (Figure 1) (Bolognia et al., 2012; Bouwstra and Ponec, 2006; Lampe *et al.*, 1983; Hachem *et al.*, 2003; Elias et al., 2006; Shah *et al.*, 2014; Jain, 2008).

The lipid-rich, hydrophobic, extracellular space of the stratum corneum is predominated by ceramides, cholesterol, and free fatty acids (Bouwstra and Ponec, 2006; Shah *et al.*, 2014). This extracellular space is formed by the conversion of lipids extruded from lamellar bodies in the stratum granulosum (i.e., glucosylceramides, sphingomyelin, cholesterol, and phospholipids). The conversion of these precursor lipids into their final end products occurs mainly by the following enzymes, which are also extruded from lamellar bodies: β-glucocerebrosidase, acid sphingomyelinase, secretory phospholipase A2, and proteases. In contrast to the extracellular space of the stratum corneum, the extracellular space in the layers including and between the stratum basale and the stratum granulosum consists of a hydrophilic environment predominated by proteinaceous molecules such as desmosomes (Elias *et al.*, 1977). Because of the importance of the stratum corneum lipids in barrier function, it is likely that there are many enhancers/excipi-

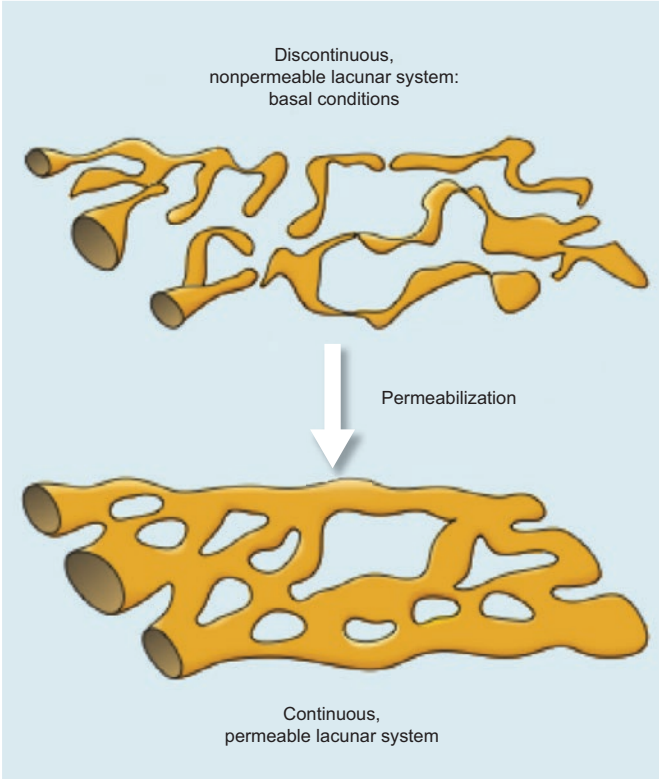

Figure 2. "Pore" pathway within the stratum corneum. Aqueous pores represent discontinuous lacunar domains formed by the degradation of corneodesmosomes. Under certain conditions, such as extensive hydration, occlusion, and sonophoresis, these pores enlarge, extend, and connect, creating a continuous pathway through the stratum corneum. Adapted from Bolognia et al. (2012) with permission from Elsevier.