

including the effects of skin condition; age and blood flow of the individual; and intraindividual variation, including the differences between anatomic sites (Noonan and Gonzalez 1990; Wester and Maibach 1993).

It is important to review the relevance of percutaneous absorption as a topic of ongoing research because of its applicability (and benefit) to current practices of pharmaceutical delivery. Percutaneous absorption has gained traction with the surfacing of new research and has the potential to alter the methods of drug delivery in modern medicine (Blattner et al. 2014).

8.1.3 WHAT IS THE SIGNIFICANCE OF A CORRELATION BETWEEN TEWL AND PERCUTANEOUS ABSORPTION?

The extensive procedures required to measure percutaneous absorption versus TEWL enhance our interest to find a correlation between the two measurements to more easily assess skin barrier function and should aid in the understanding and development of penetration enhancers. Recent studies have surmised that heating the skin results in an increased rate of percutaneous absorption of water. In skin diseases like AD and psoriasis, there is increased TEWL as compared to healthy skin. Not all measurements of TEWL are identical in results and should thereby be evaluated further for aspects that may have been overlooked or need further exploration. For example, tape stripping is a widely used method to measure percutaneous penetration of water, limited by its inability to quantify water molecule movement through corneocytes. Barrier function approximations are frequently measured with TEWL quantities and tape stripping by way of gradual corneocyte removal. However, according to a study by van der Molen et al. (1997), histological sections of skin still contained nonstripped skin in the furrows despite 20 replications of tape stripping (van der Molen et al. 1997). All of this becomes important when assessing the relationship between TEWL and percutaneous absorption, which will be further unpacked in this chapter (Blattner et al. 2014).

In an earlier version of this chapter by Levin and Maibach in 2005, nine studies investigating the correlation between TEWL and percutaneous absorption were evaluated. Of the nine studies reviewed, a majority demonstrated a significant quantitative correlation and a few found quantitative correlation. At that time, it was thought that the correlation between TEWL and percutaneous absorption may not hold for in vitro experimentation models, extremely lipophilic compounds, or possibly experiments performed on animal skin. Since then, several other studies have been published that investigated the relationship between TEWL and percutaneous absorption using a lipophilic compound (Hui et al. 2012), in vitro models (Elkeeb et al. 2010; Elmahjoubi et al. 2009; Hui et al. 2012, Guth 2015), and animal skin (Elmahjoubi et al. 2009). All of these studies demonstrated a significant quantitative correlation. In the next section, we review fourteen studies investigating the correlation between TEWL and percutaneous absorption.

8.2 PERTINENT STUDIES INVESTIGATING THE CORRELATION BETWEEN TEWL AND PERCUTANEOUS ABSORPTION

Oestmann et al. (1993) investigated the correlation between TEWL and hexyl nicotinate (HN) penetration parameters in humans. The penetration of HN was indirectly measured using laser-Doppler flowmetry (LDF), which quantifies the increase in cutaneous blood flow (CBF) caused by penetration of HN, a vasodilatory substance. Lipophilic HN was chosen over hydrophilic methyl nicotinate because HN is a slower penetrant (since it is a lipoid compound), hence making it easier to distinguish an intact barrier from an impaired barrier. Again, it is expected that in an impaired barrier, compounds are more rapidly absorbed. The LDF parameters of initial response time (t_0) and time to maximum response (t_{max}) were compared with corresponding TEWL values, and a weak quantitative negative correlation was found ($r = -0.31$, $r = -0.32$). This correlation suggests that when individual initial response time, t_0 , was quick, the skin barrier was impaired,