Factors Influencing Transepidermal Water Loss Measurements Used to Test Skin Barrier Integrity In Vitro: A Literature Review

Ying Jiang[1], Matteo A. Simamora[2], Tannaz Ramezanli[1], Sam G. Raney[1]

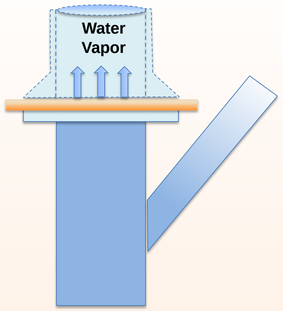
[1]Division of Therapeutic Performance I, Office of Research and Standards, Office of Generic Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD, USA

[2]Thomas Wootton High School, Rockville, MD, USA

Introduction

Transepidermal water loss (TEWL) measurements are used to distinguish competent (intact) vs. compromised skin sections for in vitro permeation testing (IVPT). The measurements are expected to be done with skin sections mounted on diffusion cells, where the underside of the skin is in contact with the receptor solution. In this context of use, the TEWL measurement probes may need specialized designs or adaptors to optimize the probe interface with the skin area being monitored. The current literature review aimed to delineate factors that could influence TEWL measurements for in vitro skin barrier integrity testing.

TEWL (in vitro)



- "*TEWL is the diffusion of condensed water through the stratum corneum (SC), whereas TEWL methods measure water vapour flux in the air above the SC.*" (Imhof et al.)

- Common practical unit: g/m^2/hr
- Water vapor flux density (J)

$$J = \frac{Mass\ of\ Water}{Area \times Time}$$ (Imhof et al.)

Figure 1. TEWL measurement device probes with three operational mechanisms: (A) open chamber, (B) closed chamber, and (C) closed condenser chamber

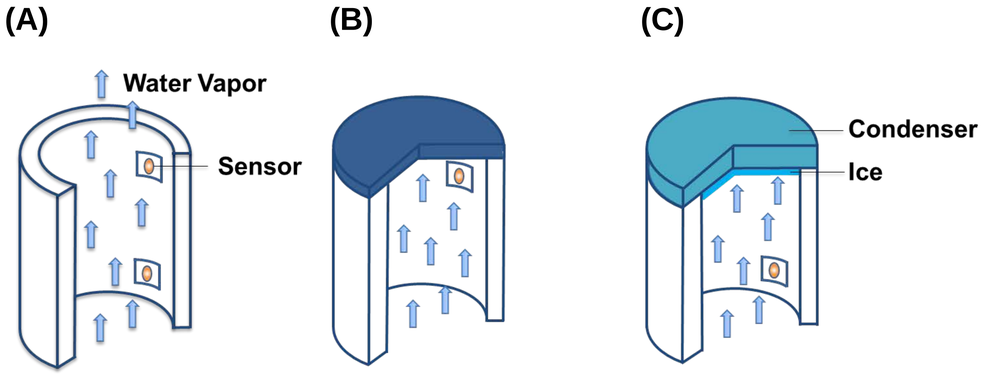


Figure 1 was redrawn from a publication by Alexander et al.

Figure 2. Representative adaptations (by manufacturers) of TEWL measurement devices for in vitro use

Open chamber

Picture courtesy of Courage+Khazaka electronic GmbH

Closed chamber

Picture courtesy of Delfin technologies

Closed condenser chamber

Picture courtesy of Biox Systems Ltd

Factors Influencing Transepidermal Water Loss Measurements Used to Test Skin Barrier Integrity In Vitro: A Literature Review

CONTROLLED RELEASE SOCIETY CRS 2021 VIRTUAL ANNUAL MEETING BREAKTHROUGH DELIVERY SCIENCE July 25-29, 2021

FDA U.S. FOOD & DRUG ADMINISTRATION

Methods

Literature in the PubMed database related to TEWL measurement (published in November 2020, or before) were retrieved (based on key terms including TEWL, transdermal epidermal water loss, trans-epidermal water loss, transepidermal water loss) and screened to select those involving a relevant technique/device used for in vitro studies with excised human skin. From the individual studies, method parameters and measured values were summarized and compared. Information on relevant device manufacturers' websites were also reviewed for commercially available TEWL measurement device.

Results

It was apparent that TEWL skin barrier integrity test results reported may have been influenced by factors related to ambient conditions, devices, diffusion cells, skin sections, and the placement of the device. Independently, the relevant method parameters in individual studies were found to be variable and/or not sufficiently well described, which may explain some of the differences in the reported TEWL values (baseline ranging from <1 g/m^2/hr to ~ 50 g/m^2/hr), even when the same TEWL measurement device was used. In particular, it was not always clear whether or not the TEWL was measured under conditions where the skin surface temperature was at 32°C ± 1°C (to align with that in vivo). Additionally, differences in diameters and/or interface geometries between TEWL measurement devices and skin/donor compartments were often not reported in detail, and unreported factors could have contributed to differences in TEWL measurements.

Table 1. Factors Influencing TEWL Measurements That Are Used to Test Skin Barrier Integrity In Vitro

	Ambient condition	Device	Diffusion cells	Skin sections	Placement of the device
Factors influencing the production of TEWL	• Ambient air temperature • Relative humidity • Light source	• Operational mechanism o Impact on the microclimate above the skin surface	• Receptor solution temperature o Impact on the skin surface temperature	• Skin surface temperature • Skin source, type, preparation • Skin equilibration	
Factors influencing the measurement of TEWL	• Ambient air movements and turbulence	• Operational mechanism o Susceptibility to the influence of the ambient conditions • Probe temperature • Calibration • Probe aging • Use of in vitro adapters	• Consistency of the height of the donor compartment o Impact on the distance between the probe and the skin surface		• Alignment of the diameters of the probe orifice and the skin area being measured (in certain circumstances) • Consistency of the geometry of measurement

CONTROLLED RELEASE SOCIETY CRS 2021 VIRTUAL ANNUAL MEETING BREAKTHROUGH DELIVERY SCIENCE July 25-29, 2021

Factors Influencing Transepidermal Water Loss Measurements Used to Test Skin Barrier Integrity In Vitro: A Literature Review

FDA U.S. FOOD & DRUG ADMINISTRATION

Results

Table 2. Summary of Key Method Parameters from Individual Studies

Operational Mechanism	Ambient temperature and humidity	Receptor solution temperature	Skin surface temperature	Alignment of the device in relation to the donor compartment and/or the skin section
Open chamber (16 studies)	• 9 did not report (Brugués et al., Cristiano et al., Betz et al., D'Angelo Costa et al., Elkeeb et al., Parra et al., Dabboue et al., Osman-Ponchet et al., Suñer-Carbó et al.) • 5 reported in ranges of 18-28°C, 25-50% (Chilcott et al., Garcia et al., Kopečná et al., 2017a, Kopečná et al., 2017b, Kopečná et al., 2019) • 1 reported room temperature, controlled humidity (Verbaan et al.) • 1 reported 32±1°C, 40-60% (Heylings et al.)	• 3 did not report (Cristiano et al., Verbaan et al., Elkeeb et al.) • 8 reported ~32°C (Brugués et al., Parra et al., Heylings et al. (Incubator), D'Angelo Costa et al., Kopečná et al., 2019, Suñer-Carbó et al., Kopečná et al., 2017a, Kopečná et al., 2017b) • 1 reported 35°C (Chilcott et al.) • 4 reported ~37°C (Dabboue et al., Garcia et al., Betz et al., Osman-Ponchet et al.)	• 10 did not report (Brugués et al., 2015, Cristiano et al., 2020, Verbaan et al., 2007, D'Angelo Costa et al., 2018, Parra et al., Osman-Ponchet et al., 2017, Kopečná et al., 2019, Suñer-Carbó et al., 2019, Kopečná et al., 2017a, Kopečná et al., 2017b) • 6 reported ~32°C (Garcia et al., Heylings et al. (Incubator), Chilcott et al., Betz et al., Elkeeb et al., Dabboue et al. **(measured)**)	• 6 did not report (Brugués et al., Osman-Ponchet et al., Suñer-Carbó et al., Verbaan et al., Betz et al., Kopečná et al., 2017b) • 3 reported probe placed on skin (Heylings et al., D'Angelo Costa et al., Parra et al.) • 1 reported probe placed on top of donor compartment (Dabboue et al.) • 1 reported probe (specialized for in vitro use) placed on skin (Cristiano et al.) • 5 reported probe placed on an in-house made adapter (Garcia et al., Chilcott et al., Elkeeb et al., Kopečná et al., 2019, Kopečná et al., 2017a)
Closed chamber (9 studies)	• 6 did not report temperature and 8 did not report relative humidity (Elkeeb et al., Guth et al., Manda et al., Jacques-Jamin et al., Hopf et al., Nguyen & Banga, Zhang et al.(temperature reported), Badran et al.(temperature reported)) • 2 reported ~25°C or room temperature (Badran et al., Zhang et al.) • 1 reported 24±2°C, 30±10% (Atrux-Tallau et al.)	• 2 did not report (Elkeeb et al., Jacques-Jamin et al.) • 3 reported ~32°C (Guth et al., Badran et al., Hopf et al.) • 1 reported ~34°C (Zhang et al.) • 3 reported ~37°C (Atrux-Tallau et al., Manda et al., Nguyen & Banga)	• 5 did not report (Guth et al., Manda et al., Badran et al., Jacques-Jamin et al., Hopf et al.) • 4 reported ~32°C (Atrux-Tallau et al., Zhang et al., Elkeeb et al., Nguyen & Banga)	• 3 did not report (Jacques-Jamin et al., Hopf et al., Nguyen & Banga) • 1 reported probe placed on skin (Zhang et al.) • 3 reported probe placed on top of donor compartment (Atrux-Tallau et al., Zhang et al., Guth et al.) • 1 reported probe placed on top of donor compartment with manufacturer's in vitro adapter (Manda et al.) • 2 reported probe placed on an in-house made adapter (Elkeeb et al., Badran et al.)
Closed condenser chamber (3 studies)	• 2 did not report (Gomaa et al., Elkeeb et al.) • 1 reported ~24°C, 40–50% (Hui et al.)	• 2 did not report (Elkeeb et al., Hui et al.) • 1 reported 37±0.5°C (Gomaa et al.)	• 1 did not report (Gomaa et al.) • 2 reported 32°C (Elkeeb et al., Hui et al.)	• 1 reported probe placed on top of donor compartment with manufacturer's in vitro adapter (Gomaa et al.) • 2 reported probe placed on an in-house made adapter (Elkeeb et al., Hui et al.)

References

Alexander et al. J Invest Dermatol. 2018;138(11):2295-300
Atrux-Tallau et al. Arch Dermatol Res. 2007;299(10):507-11
Badran et al. Eur J Pharm Med Res. 2009;36(4-5):511-23
Betz et al. Int J Pharm. 2001;228(1-2):147-59
Brugués et al. Nanomedicine. 2015;10(2):227-40
Chilcott et al. J Invest Dermatol. 2002;118(5):871-875
Cristiano et al. J Pharm Biomed Anal. 2020;15;186:113295
Dabboue et al. Biomed Res Int. 2015
D'Angelo Costa et al. AAPS PharmSciTech. 2018;19(5):2418-25
Elkeeb et al. Skin Res Technol, 2010;16(1):9-15
Garcia et al. Int J Cosmet Sci. 2002;24:25-34
Gomaa et al. Toxicol In Vitro. 2010;24(7):1971-8
Guth et al. Toxicol In Vitro. 2015;29(1):113-23
Heylings et al. Toxicol In Vitro. 2001;15(4-5):597-600
Hopf et al. Toxicol Lett. 2013;224(1):47-53
Hui et al. Skin Res Technol. 2011;18(1):108-13
Imhof et al. Int J Cosmet Sci. 2009;31(2):97-118
Jacques-Jamin et al. Skin Pharmacol Physiol. 2017;30(2):55-65
Kopečná et al. Pharm Res. 2017a;34(3):640-653
Kopečná et al. Pharm Res. 2017b;34(10):2097-2108
Kopečná et al. Sci Rep. 2019;9(1):1-12
Manda et al. J Pharm Sci. 2014;103(6):1638-42
Nguyen and Banga. Pharmaceutics. 2018;10(3):117
Osman-Ponchet et al. Dermatol Ther. 2017;7(3):407-15
Parra et al. Int J Pharm. 2016;501(1-2):10-17
Suñer-Carbó et al. Int J Pharm. 2019;11(2):66
Verbaan et al. J Control Release. 2007;117(2):238-245
Zhang et al. J Control Release. 2018;51:129-35

Conclusions

Based on inferences we drew from our review of the literature, we have identified and summarized factors that reportedly have the potential to influence the results of a TEWL skin barrier integrity test, and considered the implications of (not) controlling these factors in the method parameters used for individual studies in the literature. Given that there are many potential factors that can influence TEWL measurements, suitable acceptance criteria in individual studies may depend somewhat on the specific devices, method parameters, and skin that are used in a study.

Acknowledgement and Disclaimer

This project was supported in part by an appointment (Ying Jiang) to the Research Participation Program at the FDA Office of Research and Standards, Office of Generic Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, administered by the Oak Ridge Institute for Science and Education through an interagency agreement between the U.S. Department of Energy and FDA. The views expressed in this poster are those of the authors and should not be construed to represent FDA's views or policies.