The Transient Dermal Exposure II: Post-Exposure Absorption and Evaporation of Volatile Compounds

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Received 7 October 2014; revised 3 December 2014; accepted 11 December 2014

Published online 21 January 2015 in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/jps.24334

ABSTRACT: The transient dermal exposure is one where the skin is exposed to chemical for a finite duration, after which the chemical is removed and no residue remains on the skin's surface. Chemical within the skin at the end of the exposure period can still enter the systemic circulation. If it has some volatility, a portion of it will evaporate from the surface before it has a chance to be absorbed by the body. The fate of this post-exposure "skin depot" is the focus of this theoretical study. Laplace domain solutions for concentration distribution, flux, and cumulative mass absorption and evaporation are presented, and time domain results are obtained through numerical inversion. The Final Value Theorem is applied to obtain the analytical solutions for the total fractional absorption by the body and evaporation from skin at infinite time following a transient exposure. The solutions depend on two dimensionless variables: χ, the ratio of evaporation rate to steady-state dermal permeation rate; and the ratio of exposure time to membrane lag time. Simple closed form algebraic equations are presented that closely approximate the complete analytical solutions. Applications of the theory to the dermal risk assessment of pharmaceutical, occupational, and environmental exposures are presented for four example chemicals. © 2015 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 104:1499–1507, 2015
Keywords: absorption potential; transdermal; passive diffusion/transport; percutaneous; skin; solvent evaporation

INTRODUCTION

Recent analyses have advanced our understanding of the absorption of chemicals in contact with skin from finite dose[1–5] and transient exposures.[6,7] The former is characterized as an exposure to a small (finite) dose (mass/area) of chemical, the disposition of which has been shown to depend on the relative rates of evaporation and permeation as well as the initial load. The finite dose is a good model for splash-type exposures in the workplace and also for pharmaceutical and cosmetic product applications. The transient exposure is one where the skin is exposed to chemical for a finite duration, after which the chemical is removed and no residue remains atop the surface. Chemical within the skin at the end of the exposure period can still enter the systemic circulation. If it has some volatility, a portion of it will evaporate from the skin surface before it has a chance to be absorbed by the body. As an example that is relevant to dermal risk assessment, consider bathing or showering with contaminated water. Dermal absorption proceeds for the duration of the exposure, but once the bath or shower has ended, contaminant residing within the skin may still be absorbed by the body while some may evaporate into the surrounding air. The fate of this post-exposure "skin depot" is the focus of this theoretical study.

Frasch and Barbero[7] provided analytical solutions for total mass absorbed by the body (exposure duration plus post-exposure) for the extreme cases of non-volatile and infinitely volatile chemicals. N'Dri-Stempfer and Bunge[6] presented finite difference post-transient exposure solutions for chemicals of varying volatility. Based on the numerical results, they derived a four-parameter empirical equation to predict post-exposure evaporation expressed as a fraction of the mass residing within the membrane at the conclusion of the exposure time. Herein, we derive the complete analytical solutions for fractional absorption by the body and evaporation from skin for variable volatility. In this study, as in previous ones, the skin is considered to be a single pseudo-homogeneous membrane.

THEORY

It is assumed here that the skin is transiently exposed to a (possibly) volatile chemical. At the end of the exposure period, the skin is efficiently decontaminated such that zero residual chemical remains on the surface. We wish to determine the disposition of chemical residing within the skin following this exposure.

With the exception of highly lipophilic chemicals, the main barrier property of the skin is imparted by the stratum corneum (SC). In its simplest form, the SC may be considered to be a uniform effective medium of thickness h, occupying the space between $x = 0$ (the skin surface) and $x = h$ (bottom of tissue). The permeant has an effective diffusivity D that does not vary with position or time. This implies that neither the permeant nor its vehicle alter the SC permeability. The SC, initially free of chemical, is exposed to a constant concentration in vehicle C_v for a specified duration t_{exp}. It is assumed that the chemical does not bind to the SC and that the dermal vasculature acts as a perfect sink at the bottom of the tissue.

With these stipulations, post-exposure ($t \geq t_{exp}$) permeant transport is governed by the one-dimensional diffusion

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This article contains supplementary material available from the authors upon request or via the Internet at http://onlinelibrary.wiley.com/.

Journal of Pharmaceutical Sciences, Vol. 104, 1499–1507 (2015)
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equation:

$$\frac{\partial C}{\partial t} = D\frac{\partial^2 C}{\partial x^2} \quad 0 \le x \le h, \tag{1}$$

with the initial condition:

$$C(x,0) = C_0(x) = K_{\mathrm{mv}}C_{\mathrm{v}}\left[1 - \frac{x}{h} - \frac{2}{\pi}\sum_{n=1}^{\infty}\frac{1}{n}\sin\left(\frac{n\pi x}{h}\right)\exp\left(\frac{-n^2\pi^2}{6}\frac{t_{\mathrm{exp}}}{t_{\mathrm{lag}}}\right)\right], \tag{2}$$

where K_{mv} is the membrane–vehicle partition coefficient and the lag time $t_{\mathrm{lag}} = \frac{h^2}{6D}$. The boundary conditions are:

$$C(h,t) = 0$$
$$D\left.\frac{\partial C}{\partial x}\right|_{x=0} = \gamma C(0,t), \tag{3}$$

where

$$\gamma = \chi\frac{D}{h}. \tag{4}$$

The parameter χ is the dimensionless ratio of the evaporation rate to the steady-state dermal absorption rate of the permeant, and is discussed in detail elsewhere.[2,6] Physically, χ describes the post-exposure conditions at the skin surface and its value, depending on the situation, can vary from zero, representing zero flux from the skin surface, to infinity, which corresponds to zero concentration (sink conditions) on the skin surface. In addition to representing chemicals that evaporate rapidly from the skin surface, $\chi \to \infty$ mathematically describes a situation in which a chemical is removed from the skin with a continuous rinse or solvent immersion. In instances where chemical volatility is equated with χ in this manuscript, it is understood that volatility is relative to the dermal absorption rate. Any two chemicals may have similar evaporation rates, but χ will differ if the dermal absorption rates differ.

The initial concentration distribution specified by Eq. (2) is given by Crank.[8] Note that the initial mass (per unit area) within the SC, that is, the total mass at the end of the exposure time, is:

$$m_0 = \int_0^h C_0(x)\,dx = 3k_{\mathrm{p}}C_{\mathrm{v}}t_{\mathrm{lag}}\left[1 - \frac{8}{\pi^2}\sum_{n=0}^{\infty}\frac{1}{(2n+1)^2}\exp\left(\frac{-(2n+1)^2\pi^2}{6}\frac{t_{\mathrm{exp}}}{t_{\mathrm{lag}}}\right)\right], \tag{5}$$

where the permeability coefficient $k_{\mathrm{p}} = K_{\mathrm{mv}}D/h$.

METHODS

The solution of Eq. (1) with associated initial and boundary conditions was undertaken using the method of Laplace transforms. Solutions for concentration distribution, flux, and cumulative mass absorption and evaporation are presented. Time domain solutions were obtained through numerical inversion of the Laplace domain equations using Scientist (MicroMath Scientific Software, St. Louis, Missouri). The Final Value Theorem was applied to obtain total cumulative mass absorption and evaporation at infinite time postexposure, expressed as fractions of the total mass within the skin at the end of the exposure time. Simple closed form algebraic equations are presented that closely approximate the complete analytical solutions. For practical applications, the time it takes for the body to absorb 90% of the total infinite-time amount was estimated.

RESULTS

The Laplace transform of Eq. (1) is:

$$\frac{d^2\hat{C}(x,s)}{dx^2} - \lambda^2\hat{C}(x,s) = \frac{-C_0(x)}{D}, \tag{6}$$

with the hat (ˆ) indicating a function of the Laplace variable s, and $\lambda = \sqrt{s/D}$. The Laplace transform of Eq. (3) is:

$$\hat{C}(h,s) = 0$$
$$\gamma\hat{C}(0,s) - D\left.\frac{d\hat{C}(x,s)}{dx}\right|_{x=0} = 0. \tag{7}$$

The solution of Eq. (6) with specified initial (Eq. (2)) and boundary (Eq. (7)) conditions is:

$$\hat{C}(x,s) = \frac{\hat{R}_0(s)\sinh[\lambda(h-x)]}{-\lambda D\cosh(\lambda h) - \gamma\sinh(\lambda h)} + \hat{C}_{\mathrm{p}}(x,s), \tag{8}$$

with

$$\hat{C}_{\mathrm{p}}(x,s) = \frac{K_{\mathrm{mv}}C_{\mathrm{v}}}{D}\left[\frac{1}{\lambda^2} - \frac{x}{\lambda^2 h} - \frac{2}{\pi}\sum_{n=1}^{\infty}\frac{\sin(k_n x)}{n\left(k_n^2+\lambda^2\right)}\exp\left(\frac{-n^2\pi^2}{6}\frac{t_{\mathrm{exp}}}{t_{\mathrm{lag}}}\right)\right], \tag{9}$$

where $k_n = n\pi/h$, and

$$\hat{R}_0(s) = \gamma\hat{C}_{\mathrm{p}}(0,s) - D\frac{d\hat{C}_{\mathrm{p}}(0,s)}{dx} = K_{\mathrm{mv}}C_{\mathrm{v}}\left[\frac{\gamma}{\lambda^2 D} + \frac{1}{\lambda^2 h} + \frac{2}{h}\sum_{n=1}^{\infty}\frac{1}{\left(k_n^2+\lambda^2\right)}\exp\left(\frac{-n^2\pi^2}{6}\frac{t_{\mathrm{exp}}}{t_{\mathrm{lag}}}\right)\right]. \tag{10}$$

$\hat{C}_{\mathrm{p}}(x,s)$ is the particular solution to Eq. (6). Its value depends on the specific form taken by the nonhomogeneous terms (here, $-C_0(x)/D$). Tables of solutions are available in a number of sources (e.g., the CRC Standard Mathematical Tables[9]).

Figure 1 shows plots of $C(x,t)$ within the membrane for various values of χ. The plots represent inverse Laplace transforms of Eq. (8). For small χ, there is little evaporation and the chemical concentration is greatest at the skin surface. The time to

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