25 Analytical and Numerical Methods in Determining the Combined Effects of Iontophoresis and Chemical Penetration Enhancers

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25.1 Introduction

Physical techniques, such as iontophoresis (Kumar and Banga 2012; Gratieri et al. 2011; Luzardo-Alvarez et al. 2001), ultrasound (phono- or sonophoresis) (Herwadkar et al. 2012; Sarheed and Abdul Rasool 2011), electroporation (Yan et al. 2010; Charoo et al. 2010), and heat (Petersen et al. 2011; Carter 2003) are used to increase molecular transport across the skin. Several articles have been devoted to understanding and describing the mechanisms of membrane permeation. During heat-enhanced transport, for example, locally applied thermal energy improves a host of factors, such as body fluid circulation, drug solubility, and skin permeability. Akomeah and co-investigators (2004) suggested that the diffusion coefficient of the drug in the vehicle depended on the temperature, and therefore could explain the increase in the delivery rate. According to other authors, the improvement in flux, following heat exposure, is the result of an increase in the fluidity of the stratum corneum lipids (Ohara et al. 1995).

In iontophoresis, transport of the drug molecules across the skin barrier is promoted by a small electric current applied to the skin. Cationic drugs are placed under the anode, while negatively charged medicaments are positioned at the cathode. A battery is included in the device to transport the drug from a donor solution into the tissue. The return electrode, immersed in a buffer

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solution, is used to close the electrical circuit (Junginger 2002). Movement of ions is due to diffusion and iontophoretic and electroosmotic components. The electroosmotic flow through aqueous channels makes it possible to deliver neutral and uncharged molecules. Important factors contributing to iontophoretic transport are the solution pH, current intensity and duration, competing ions, applied drug concentration, molecular weight, convective transport, and the mode of operation (i.e., continuous versus pulsed current) (Bronaugh and Maibach 1999).

Chemical enhancement has also been applied to alter the barrier function of the stratum corneum and increase the skin permeability. Ideally, chemical penetration enhancers (CPEs) should be nontoxic and compatible with the drugs and excipients contained in the formulation (Williams and Barry 2004). These sorption promoters include compounds such as sulfoxides, azone, pyrrolidones, fatty acids, alcohols, and essential oils (Williams and Barry 2004). This technology offers several advantages. Medications (e.g., labetalol hydrochloride) that are subject to extensive first-pass metabolism can now be delivered via the dermal route with the use of dimethyl sulfoxide (Zafar et al. 2010). Research with azone and three drugs, namely, indomethacin, ibuprofen, and sulfanilamide, shows that some compounds can improve thermodynamic activities and affinities of drug molecules to the dermal tissue (Ito et al. 1988). Terpene enhancers are also effective at increasing the percutaneous permeation of hydrophilic drugs (El-Kattan et al. 2001).

Notable efforts have been made to improve skin permeability by combining iontophoresis with chemical enhancement. Relative to passive diffusion alone, this combined strategy produced a higher flux of lidocaine hydrochloride and nicotine hydrogen tartrate across the oral mucosa compared to (Wei et al. 2012). With sodium lauryl sulfate, the use of electrical current promotes the delivery of metoprolol tartrate and results in appreciable drug retention in the skin (Nair et al. 2011). A mixture of CPEs and modulated iontophoresis leads to a 45 % enhancement in the transdermal delivery of insulin when measured against iontophoretic control (Rastogi et al. 2010).

25.2 Review of Mathematical Modeling

Whether the CPEs are incorporated into formulations or applied to the surface of a biological membrane (e.g., skin, mucosa), the system is usually modeled as diffusion through a passive membrane (Williams and Barry 2004; Okamoto et al. 1988). Okamoto et al. (1988) showed that mathematical analyses of penetration profile data could help decipher the mode of action of CPEs. Their work with 6-mercaptopurine revealed that the diffusion parameter was not influenced by the pretreatment of excised guinea pig skin but by the drug partitioning into the skin. Based on model parameters, Southwell and Barry (1983) were able to assess how two accelerants, 2-pyrrolidone, and dimethylformamide, affect the permeation of water, n-alcohols, and caffeine through the stratum corneum. Quantitative structure–activity relationship (QSAR) techniques have been implemented to select desirable structural properties of CPEs. Such efforts would help topical drug formulators to identify key features that could potentially increase skin permeability. This approach led researchers to hypothesize that intermolecular electron donor–acceptor interactions might play a role in promoting the penetration of 5-fluorouracil by terpenes (Ghafourian et al. 2004). Similarly, the enhancement property of alkanols is a function of their lipophilicity and the location of the hydroxyl group (Ding et al. 2006).

Ferry (1995) proposed a model for iontophoresis that included diffusion and migration. Charged molecules are first carried by diffusion from the solution to the surface of the skin at which point migration becomes the main mechanism for transporting the penetrant across the stratum corneum. Although the authors only conducted a steady-state analysis of the process, they were able to provide useful insights on the importance of radial transport, especially when dealing with low-density skin appendages (e.g., sweat glands, hair follicles). The modeling work also makes it possible to simulate the effect of the current intensity on the flux. However, models, such as the one studied by Keister and Kasting (1986), are more appropriate for capturing transient behaviors. The

influence of the current density on the time lag and the delivery rate can also be evaluated.

Although mathematical models may help explain the mechanisms of enhancer action and the effects of iontophoresis on drug delivery, the experimental protocols adopted are also relevant. Data are usually taken from the linear region of the cumulative amount of drug released versus the time plot to estimate partition and diffusion coefficients. These numbers help infer whether the accelerant increases the drug affinity for the skin or the ability of the medicament to permeate through the dermal layer. It is important to frame the mathematical problem in such a way that pertinent information can be extracted from these studies. Theory-guided laboratory experiments have to be conducted in a manner that reveals the relative contributions of iontophoretic and chemical enhancements. Novel applications of process dynamics and control concepts to estimate the time to establish a steady-state flux can also be incorporated in the investigations (Simon 2009). The extent to which the synergy, created by both delivery methods, influences the flux, and the time constant parameter has been assessed within the new framework (Wei et al. 2012). These topics are discussed in the next sections.

25.3 Experimental Methods

It is important to identify a priori which information is to be collected from systems using physical and chemical enhancement techniques. For studies conducted with Franz-type diffusion cells, the thickness of the biological membrane (e.g., skin, mucosa), the permeation area, and the drug concentration in the donor compartment should be recorded. These data will help in the analysis of the cumulative amount of drug released per unit area (Q). The duration of a trial and the sampling time should be adequate to allow computation of the lag time (t_{lag}), effective time constant (t_{eff}), and diffusion coefficient (D). To facilitate analysis of the data, some experiments are to be conducted in the absence of CPEs and iontophoresis. These observations provide baselines against which the effects of the enhancers can be measured. Additional tests include CPEs alone, iontophoresis alone, and the two techniques combined.

25.4 Analytical and Numerical Procedures

25.4.1 Passive or Chemically Enhanced Diffusion Across a Biological Membrane

In cases of passive and chemically enhanced diffusion, Fick's second law can be applied to analyze the process:

$$\frac{\partial C}{\partial t} = D\frac{\partial^2 C}{\partial x^2} \tag{25.1}$$

where C is the drug concentration at depth x, D represents the diffusion coefficient in the membrane, and t is the time. Initially, the membrane is free of drug:

$$C\left(x > 0, 0\right) = 0 \tag{25.2}$$

The boundary conditions are

$$C\left(0, t > 0\right) = C_s; C\left(L, t > 0\right) = 0 \tag{25.3}$$

In Eq. 25.3, C_s is the concentration at the membrane-vehicle interface and L is the membrane thickness. The drug concentration in the vehicle C_o is related to C_s by

$$C_s = KC_o \tag{25.4}$$

The flux is defined at L:

$$J = -D\frac{\partial C}{\partial x}\bigg|_{x=L} = \frac{dQ}{dt} \tag{25.5}$$

where Q is the cumulative amount of medicament released and K is the vehicle/stratum corneum partition coefficient. An expression for Q is developed by solving the system formed by Eqs. 25.1, 25.2, 25.3, and 25.5:

$$Q = LC_s\left[\frac{tD}{L^2} - \frac{1}{6} - \frac{2}{\pi^2}\left(\sum_{n=1}^{\infty}\frac{(-1)^n \exp\left[-n^2\pi^2\frac{tD}{L^2}\right]}{n^2}\right)\right] \tag{25.6}$$

The steady-state flux J_{ss} and the cumulative amount of drug released at long time Q_{ss} are

$$J_{ss} = \frac{DC_s}{L}, \tag{25.7}$$

and

$$Q_{ss} = LC_s\left(\frac{tD}{L^2} - \frac{1}{6}\right) \tag{25.8}$$

respectively. The lag time t_{lag} is given by

$$t_{lag} = \frac{L^2}{6D} \tag{25.9}$$

Besides t_{lag}, the effective time constant t_{eff} can also estimate the time elapsed before reaching J_{ss} (Collins 1980; Simon 2009):

$$t_{eff} = \frac{\lim\limits_{s\to 0}\left(\frac{J_{ss}}{s^2} + \frac{d\bar{J}(s)}{ds}\right)}{\lim\limits_{s\to 0}\left(\frac{J_{ss}}{s} - \bar{J}(s)\right)} \tag{25.10}$$

or

$$t_{eff} = \frac{7L^2}{60D} \tag{25.11}$$

in the case of passive diffusion. In Eq. 25.10, $\bar{J}(s)$ is the Laplace transform of J. The permeability coefficient P, often used in skin absorption studies, incorporates the effects of K, D, and L:

$$P = \frac{KD}{L} = \frac{J_{ss}}{C_o} \tag{25.12}$$

25.4.2 Iontophoretic Drug Transport Across a Biological Membrane

The following equation can be used to study iontophoretic drug transport across a membrane (Keister and Kasting 1986):

$$\frac{\partial C}{\partial t} = D\frac{\partial^2 C}{\partial x^2} - \frac{\gamma D}{L}\frac{\partial C}{\partial x} \tag{25.13}$$

where γ is a parameter which represents the effects of the electric field. Consideration of Eqs. 25.2 and 25.3 leads to the following expression for the cumulative amount of drug released (Wei et al. 2012; Simon 2009; Keister and Kasting 1986):

$$Q = \frac{DC_s}{L}\frac{\gamma}{1-e^{-\gamma}}\left\{t + \frac{2L^2}{D}\frac{\sinh\left(\frac{\gamma}{2}\right)}{\frac{\gamma}{2}}\sum_{n=1}^{\infty}\frac{n^2\pi^2(-1)^n}{\left(\frac{\gamma^2}{4}+n^2\pi^2\right)^2}\left[1-\exp\left(-\frac{\left(\frac{\gamma^2}{4}+n^2\pi^2\right)Dt}{L^2}\right)\right]\right\} \tag{25.14}$$

Similar to the case of passive diffusion, the following functions were derived (Simon 2009; Keister and Kasting 1986):

$$J_{ss} = \frac{DC_s}{L}\frac{\gamma}{1-e^{-\gamma}}, \tag{25.15}$$

$$Q_{ss} = \frac{DC_s}{L}\frac{\gamma}{1-e^{-\gamma}}\left[t + \frac{L^2}{D}\frac{2\sinh\left(\frac{\gamma}{2}\right) - \gamma\cosh\left(\frac{\gamma}{2}\right)}{\gamma^2\sinh\left(\frac{\gamma}{2}\right)}\right], \tag{25.16}$$

$$t_{lag} = -\frac{L^2}{D}\frac{2\sinh\left(\frac{\gamma}{2}\right) - \gamma\cosh\left(\frac{\gamma}{2}\right)}{\gamma^2\sinh\left(\frac{\gamma}{2}\right)} \tag{25.17}$$

and

$$t_{eff} = \frac{L^2\,\mathrm{csch}^2\left(\frac{\gamma}{2}\right)\left(3\gamma^2 - 2\sinh(\gamma)\gamma + \left(\gamma^2-4\right)\cosh(\gamma) + 4\right)}{4D\gamma^2\left(\gamma\coth\left(\frac{\gamma}{2}\right) - 2\right)} \tag{25.18}$$

25.5 Results

For systems using passive diffusion alone, the lag time method is adopted to calculate C_s and D (Fig. 25.1). The affinity of the skin for the drug is assessed by computing the partition coefficient K. The flux reaches 98 % of its steady-state value at $4t_{eff}$. This result is typical of a process that can be approximated by a first order system. One of the advantages of using t_{eff} as a performance criterion is the possibility of estimating the time elapsed before achieving a desired therapeutic flux. For controlled release technology, the approach can also help identify process conditions that may need to be adjusted to meet a target delivery rate (Simon 2009).

After applying a CPE to the membrane, changes in the drug diffusivity or its partitioning behavior would clarify the transport process. The direct calculations of K and D allow scientists to develop more efficient methods to design and assess chemicals that could promote drug transport through the skin. By computing partition and diffusion ratios after and before skin treatment, Khan et al. (2011) was able to hypothesize on the mechanism by which five, 9-dimethyl-2-cyclopropyl-2-decanol and tetrahydrogeraniol increased the percutaneous penetration of 5-FU and tramadol hydrochloride (Khan et al. 2011). The increased K value might be due to a change in the structure of the stratum corneum lipid bilayers, while a modification of the intercellular lipid regions might be responsible for the increased diffusion coefficient.

Three parameters need to be estimated in iontophoretic drug delivery across a polymer membrane: C_s, D, and γ. Based on previous work, the electric field is assumed to have negligible influence on the diffusion coefficient obtained from passive transport experiments (Tojo 2003; Simon et al. 2006). In addition, an increase in the surface concentration has been reported after the onset of iontophoresis. This effect was verified by a skin-stripping method in the case of verapamil (Tojo 2003). Thus, an apparent partition coefficient should be determined using Eq. 25.4. The parameter γ corresponds to the intersection of the function

$$f(\gamma) = -\frac{L^2}{D}\frac{2\sinh\left(\frac{\gamma}{2}\right) - \gamma\cosh\left(\frac{\gamma}{2}\right)}{\gamma^2\sinh\left(\frac{\gamma}{2}\right)} - t_{lag} \tag{25.19}$$

with the γ -axis. Note that t_{lag} is known from the plot of experimental $Q(t)$ versus the time. Finally, C_s is obtained from the experimental slope predicted by Eq. 25.16 (Simon et al. 2006):

$$\text{Slope} = \frac{DC_s}{L}\frac{\gamma}{1-e^{-\gamma}} \tag{25.20}$$

An illustration is shown in Fig. 25.2. The study focused on the delivery of amitriptyline HCl through cadaver human skin placed

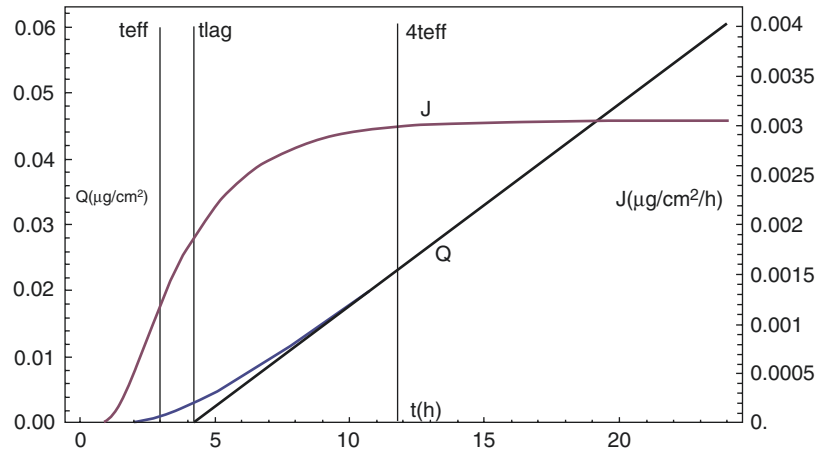

Fig. 25.1 Transient flux and cumulative amount of drug released by passive diffusion. The effective time constant and lag time are represented by t_{eff} and t_{lag}, respectively

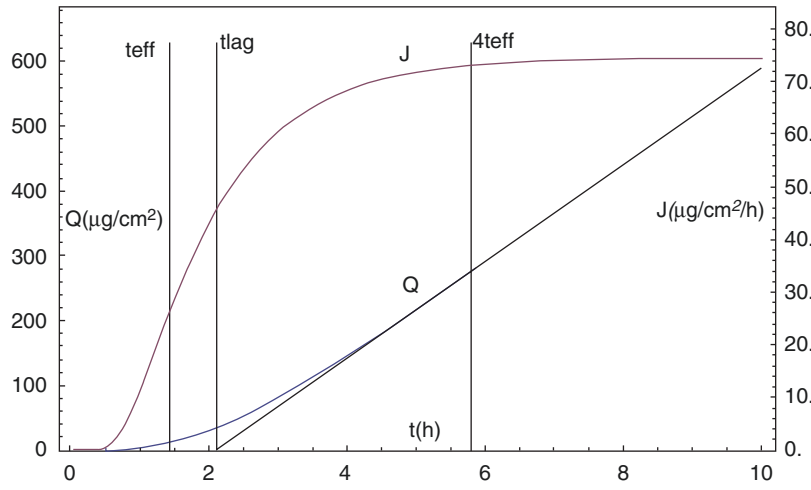

Fig. 25.2 Dynamic flux and cumulative amount of drug released by iontophoresis. The effective time constant and lag time are represented by t_{eff} and t_{lag}, respectively

between two Franz diffusion cells (Simon et al. 2006; Wang 2004). The following parameters were obtained by the procedure outlined above: $D = 1.79 \times 10^{-4}\,\mathrm{cm^2/h}$, $\gamma = 2.50$, and $C_s = 7640\,.\mathrm{g/ml}$. The steady-state flux, lag time, and effective time constant are 74.6 μg/cm²h, 2.1 h and 1.4 h, respectively.

A systematic analysis can be conducted to help link the properties of the device to its performance resulting from the use of iontophoresis and pretreatment of a membrane with a CPE. The flux ratio after applying the CPE is:

$$\frac{J_{ss-ch}}{J_{ss-c}} = \frac{D_{ch}C_{s-ch}}{D_c C_{s-c}} = \frac{D_{ch}}{D_c}\frac{K_{ch}}{K_c} \qquad (25.21)$$

where the subscripts "*c*" and "*ch*" correspond to control and CPEs, respectively. The following equation is appropriate to contrast the effect of the electric field, "*el*," with that of the control:

$$\frac{J_{ss-el}}{J_{ss-c}} = \frac{D_{el}C_{s-el}\dfrac{\gamma}{1-e^{-\gamma}}}{D_c C_{s-c}} = \frac{C_{s-el}}{C_{s-c}}\frac{\gamma}{1-e^{-\gamma}} = \frac{K_{el}}{K_c}\frac{\gamma}{1-e^{-\gamma}} \qquad (25.22)$$

since $D_{el} = D_c$ (Tojo 2003; Simon et al. 2006), Eq. 25.23 can be used to study the influence of iontophoresis without CPEs and the mechanisms of action of CPEs:

$$\frac{J_{ss-el}}{J_{ss-ch}} = \frac{D_{el}C_{s-el}\dfrac{\gamma}{1-e^{-\gamma}}}{D_{ch}C_{s-ch}} = \frac{D_c}{D_{ch}}\frac{C_{s-el}}{C_{s-ch}}\frac{\gamma}{1-e^{-\gamma}} = \frac{D_c}{D_{ch}}\frac{K_{el}}{K_{ch}}\frac{\gamma}{1-e^{-\gamma}} \qquad (25.23)$$

The following equation is defined to help assess the impact of iontophoresis combined with CPEs on drug delivery relative to the use of CPEs alone:

$$\frac{J_{ss-el-ch}}{J_{ss-ch}} = \frac{D_{ch}C_{s-el-ch}\dfrac{\gamma_{ch}}{1-e^{-\gamma_{ch}}}}{D_{ch}C_{s-ch}} = \frac{C_{s-el-ch}}{C_{s-ch}}\frac{\gamma_{ch}}{1-e^{-\gamma_{ch}}} = \frac{K_{el-ch}}{K_{ch}}\frac{\gamma_{ch}}{1-e^{-\gamma_{ch}}} \qquad (25.24)$$

To compare iontophoresis combined with CPEs to the control, we have:

$$\frac{J_{ss-el-ch}}{J_{ss-c}} = \frac{D_{ch}C_{s-el-ch}\dfrac{\gamma_{ch}}{1-e^{-\gamma_{ch}}}}{D_c C_{s-c}} = \frac{D_{ch}}{D_c}\frac{C_{s-el-ch}}{C_{s-c}}\frac{\gamma_{ch}}{1-e^{-\gamma_{ch}}} = \frac{D_{ch}}{D_c}\frac{K_{el-ch}}{K_c}\frac{\gamma_{ch}}{1-e^{-\gamma_{ch}}} \qquad (25.25)$$

Ratios of effective time constants can be computed in a similar manner and help determine the extent to which the enhancer affects the time needed to reach the desired delivery rate.

Conclusions

Mathematical procedures to study the effects of iontophoresis and chemical enhancers were proposed. In collecting permeation data, attention should be paid to the sampling time and the duration of the experiments. This will allow the computation of the lag time (t_{lag}), effective time constant (t_{eff}), diffusion coefficient (D), electric field parameter (γ), and the vehicle/stratum corneum partition coefficient (K). For passive transport, in the presence or absence of a chemical enhancer, the lag time technique can be applied to estimate t_{lag}, K, and D. Except for the diffusion coefficient, the other parameters are expected to change after iontophoresis. A graphical method can be implemented to compute γ, which allows the calculation of K from the slope of the linear section of the cumulative amount of drug released against the time plot. Two examples were given to illustrate the methodologies. Expressions that relate flux enhancement ratios with properties of controlled release devices were developed. Similar parameters can be obtained for the time constants to assess whether the time to achieve the target flux has decreased.

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