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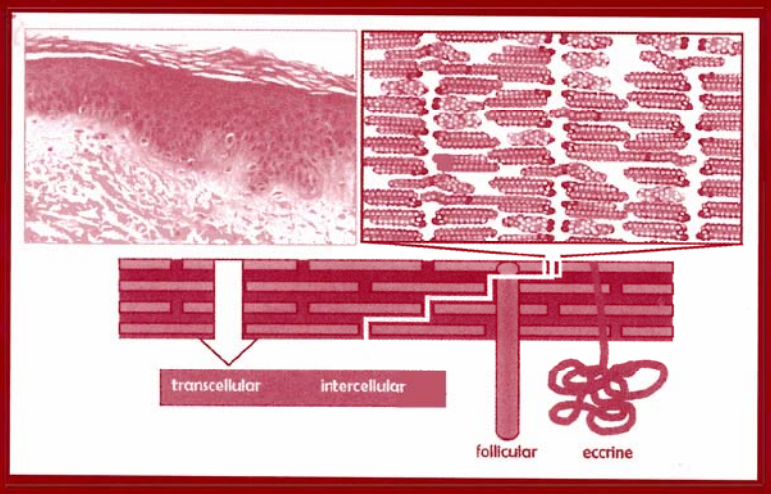
Transdermal Drug Delivery

Second Edition, Revised and Expanded



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tion, which elicits a systemic effect. This route has a number of attractions, and an accurate and predictive model would be invaluable in the selection and evolution of appropriate transdermal drug candidates. Equally, there are also chemicals, the absorption of which in significant amounts is clearly undesirable. Compounds such as pesticides are obvious examples, but there are other materials, present perhaps as formulation excipients, that could also be detrimental. An appropriate mathematical model would allow a reliable risk assessment to be made before in vivo evaluations are conducted.

There are different considerations to be taken into account depending on whether the drug is to be delivered for local action or for systemic action. Since this book concerns primarily transdermal delivery, the major emphasis will be how to ensure the transport of drug through the skin into the underlying dermal vasculature and hence the systemic circulation. For a drug to be administered transdermally, it has to be very potent, as it is unlikely that more than a few tens of milligrams per day can be delivered. To a first approximation, feasibility can be assessed from the daily dose. But, as will be seen, even for a compound like nitroglycerine, which has ideal physicochemical properties for transdermal delivery from a reasonable patch area, no more than 40 to 50 mg per day can be delivered.

In some ways, it is more difficult to assess the feasibility of topical drug delivery, as the levels required in the skin for therapeutic effect are usually unknown. For transdermal delivery, there is a well-documented and determinable end point, the plasma level required for efficacious therapy. Advances in noninvasive monitoring and microdialysis can be helpful in determining the target skin concentration for topical therapy, but data are limited, and the reliability of the methodologies involved is still in question, as the techniques remain in very much a developmental stage.

Validated mathematical models represent an economically advantageous approach for the assessment of skin permeation, and their use is recommended before full-blown in vitro and in vivo experiments are conducted. The purpose of this chapter is to examine the limitations of mathematical modeling and to consider appropriate in vitro models prior to full clinical testing.

II. FICK'S LAWS OF DIFFUSION

Considering that the skin is such a heterogeneous membrane, it is surprising that simple diffusion laws can be used to describe the percutaneous absorption process (3). Since transdermal delivery involves the application of a device over a long period of time, it is generally assumed that steady-state conditions have been reached and that the most relevant law of diffusion is therefore Fick's first law. The second law describes non–steady state diffusion and can be used to analyze

the rates of release from matrix type transdermal patches, to evaluate the lag phase prior to the establishment of steady-state conditions, and to describe concentration profiles across the skin as they evolve towards linearity.

The most quoted form of Fick's first law of diffusion describes steady-state diffusion through a membrane:

$$J = \frac{KD}{h}(c_o - c_i) \tag{1}$$

where J is the flux per unit area, K is the stratum corneum-formulation partition coefficient of the drug, and D is its diffusion coefficient in the stratum corneum of path length h; c_o is the concentration of drug applied to the skin surface, and c_i is the concentration inside the skin. In most practical situations, $c_o \gg c_i$, and Eq. (1) simplifies to

$$J = k_p c_o \tag{2}$$

where k_p ($= DK/h$) is the permeability coefficient, which has units of velocity (often quoted as cm h^{-1}), i.e., it is a heterogeneous rate constant and encodes both partition and diffusional characteristics. The input rate of the drug into the systemic circulation, from a patch of area A, is therefore given by the product

$$\text{Input rate} = A \times k_p \times c_o \tag{3}$$

The output or elimination rate from the systemic circulation equals the clearance (Cl) multiplied by the plasma concentration at steady state ($c_{p,ss}$)

$$\text{Output rate} = Cl \times c_{p,ss} \tag{4}$$

Hence Eqs. (3) and (4) may be combined to predict the drug's plasma concentration following transdermal delivery:

$$c_{p,ss} = \frac{Ak_p c_o}{Cl} \tag{5}$$

The plasma concentration achieved therefore depends directly on the area of the device, the skin permeability, and the applied concentration and is inversely related to the drug's clearance (4).

For a given drug, the clearance and the target plasma level are likely to be known, so to examine the feasibility of delivery, one needs the drug's skin permeability and its solubility, as this will give an indication of the maximum concentration that can be applied. These parameters can be estimated from basic physicochemical properties, which are typically measured during preformulation.