Parry et al. [11] has described a percutaneous absorption model in which both the donor and receptor compartments for an in vitro membrane study were well-stirred and finite. Boundary conditions similar in form to that defined by Equations (2.42) and (2.30), but with Clr = 0, were used to describe the disappearance of solute from the donor chamber into the membrane and the efflux of solute from the membrane into the receptor chamber. The resultant expression included a complex function requiring the solution of transcendental equations. It should be emphasized that this model differs from others described in this section in that it does not have a clearance term to account for sampling.

2.1.4 In Vitro Permeability Studies with a Constant Donor Concentration or Defined Input Flux and Finite Clearance of Solute from the Epidermis

The importance of receptor conditions on epidermal transport has been the subject of various studies over the last 30 years. Two models are widely used. In the first model, it is assumed that the viable epidermis or aqueous diffusion layer below the SC can exert a significant influence on skin penetration [12, 13]. The second model is one where there is an effectively desorption rate-limited step in partitioning from the membrane to the next phase (e.g., epidermis → receptor solution; SC → epidermis; epidermis → dermis). This rate constant, which we will define as k_c, and the interfacial barrier rate constant are identical if the lag time for the interfacial barrier can be assumed to be negligible. In the specific case of an aqueous diffusion layer being a barrier, $k_c = D_{aq} / l_{aq}^2$ where l_{aq} is the thickness of the layer and D_{aq} is the diffusion coefficient in the layer [13].

Guy and Hadgraft and Guy et al. [14, 15] developed a pharmacokinetic model for skin absorption based on the diffusion model with the boundary conditions defined by (1) the influx into the membrane being related to an assumed exponential decline in vehicle donor concentration and (2) the efflux from the membrane being related to first-order removal at a rate constant k_c. These authors went on to examine short and long time approximations. Kubota and Ishizaki [16] presented a more generalized diffusion model for drug absorption through excised skin by using the boundary conditions of the fluxes (1) into the skin being defined by an arbitrary function $f(t)$ and (2) out of the skin being defined by $\mathrm{Cl}C(x = h_m)$, where Cl is the clearance from the skin and $C(x = h_m)$ is the concentration of solute at the skin–system interface. They considered a boundary condition at the membrane–vehicle interface defined by an input rate into the membrane $f(t)$ together with a first-order rate constant k_c determining efflux from the membrane. Accordingly, the amount of solute absorbed across the skin $Q(t)$ at various times t is defined in the Laplace domain as:

$$\hat{Q}(s) = \frac{A}{s} \frac{k_c t_d \hat{f}(s)}{\sqrt{st_d} \sinh\left(\sqrt{st_d}\right) + k_c t_d \cosh\left(\sqrt{st_d}\right)} \tag{2.37}$$

Of particular interest in this overview is the case of a constant donor concentration (infinite donor) and sink receptor. $\hat{Q}(s)$ is then defined by:

$$\hat{Q}(s) = \frac{k_p C_v A}{s^2} \frac{k_c t_d \sqrt{st_d}}{\sqrt{st_d} \cosh \sqrt{st_d} + k_c t_d \sinh \sqrt{st_d}} \tag{2.38}$$

Figure 2.8A shows the effect of k_c (as defined by $\alpha = k_c t_d$) on the $Q(t)$ versus time profile.

It is to be noted that at long times, the linear portion of $Q(t)$ [defined by Equation (2.38)] versus t profile describes a steady-state flux J_{ss} and lag time (lag):

$$Q(t) = J_{ss} A(t - \mathrm{lag}) = C_v k_p A \frac{k_c t_d}{1 + k_c t_d} (t - \mathrm{lag}) \tag{2.39}$$

$$\mathrm{lag} = \frac{t_d}{6} \left(1 + \frac{2}{1 + k_c t_d} \right) \tag{2.40}$$