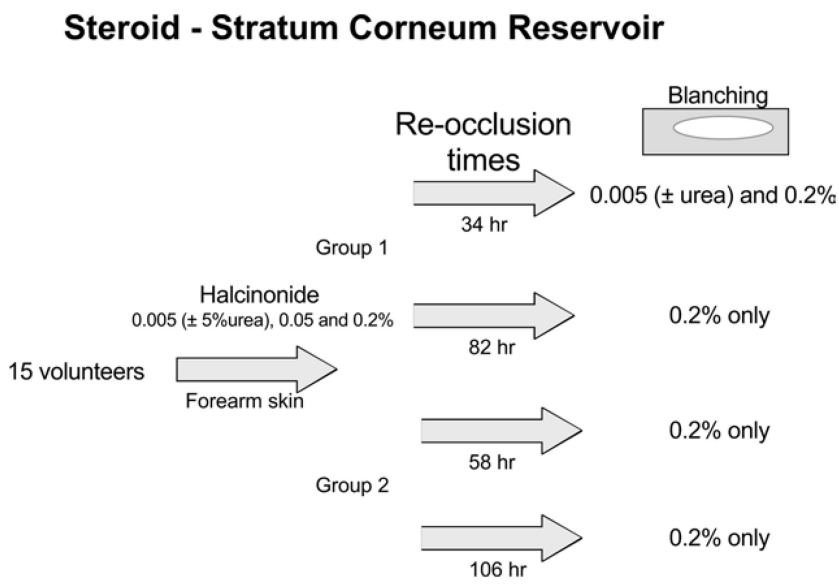

FIGURE 4.5 Time, concentration, and enhancer dependency of the reservoir effect as illustrated for halcinonide. (From Reference 25.)

it is possible that a reservoir effect will be evident with a lower steroid concentration but only for a short time. Clarys et al. (25) showed that when the enhancer urea was included in reocclusion after halcinonide 0.005%, a significant vasoconstriction was achieved when reocclusion was conducted at 34 hours but not at other later times.

Understanding changes in vasoconstriction associated with a stratum corneum reservoir effect through reocclusion or application of an enhancer at a time after the origination application is most easily achieved using an appropriate mathematical model. While a diffusion model may be the most appropriate to describe transport events in the skin and relatively easy to use when expressed in the Laplace domain (7), such a model is difficult to use when model parameters change during the time course of an experiment. Further, precise modeling is further complicated by the known steroid vasoconstrictor nonlinear topical dose–effect relationships (7). Accordingly, for this purpose, we have represented the stratum corneum and viable epidermis as simple, well-stirred compartments (Figure 4.6). We have further limited the model to situations where the reservoir has already been established so as to recognize that this model poorly predicts lag times associated with steady-state epidermal penetration (7, 26). As stated in the introduction, the model has an obvious limitation in that it assumes all of the tissues are well stirred when a diffusional process would better describe the solute transport therein.

The rate constant k_1 is related to the diffusion time, i.e., $k_1 = \pi^2 D_{sc}/4h^2_{sc}$, where D_{sc} is the diffusivity and h_{sc} is the thickness of the stratum corneum. This definition is also equivalent to $\pi^2 k_p A_s/4V_{apsc}$ as $k_p = K_{sc-ve}\, D_s/h_{sc}$, and $V_{apsc} = K_{sc-ve}\, V_{sc} = K_{sc-ve}\, A_s h_{sc}$, where V_{apsc} is the apparent distribution volume of the solute in the stratum corneum and A_s is the area of application. This constant k_1 could be further complicated by also being a function of microconstants defining other transport events in the stratum corneum. The rate constant k_2 is a function of both the diffusion time and stratum corneum–viable epidermis partition coefficient K_{sc-ve}, i.e., k_2 is equivalent to $K_{sc-ve}\, k_1 V_{sc}/V_{ve}$, where *V*ve is the volume of distribution of the solute in the viable tissue. It is apparent that when k_2 or K_{sc-ve} is large, a reservoir effect in the stratum corneum is promoted. The rate constant k_3 defines the removal of the solute from the viable tissue and can be derived from the clearance of solute from the tissue as $k_3 = CL_{ve}/V_{ve}$.