$$\frac{dM_t}{dt} = A \frac{a_v}{\delta_s}\left[\frac{D_{sc}}{h_{sc}}\right] \quad [28]$$

Where dM_t/dt is the rate of penetration, K is the stratum corneum/vehicle partition coefficient, C_V is the drug's concentration in the vehicle, A is the area of the application site, h_{SC} is the effective thickness of the skin, D_{SC} is the effective stratum corneum diffusivity, a_V is the thermodynamic activity of the drug in the vehicle, and δ_S is the effective activity coefficient of the drug in the skin barrier. The latter equation indicates that only certain terms are available for manipulation by the formulator to increase the rate of diffusion of a drug. These are K, the partition coefficient, and C_V, the drug's concentration in the vehicle. K is altered when the composition of the vehicle is altered, and C_V can be adjusted up to the level of solubility in the vehicle. Note that, for saturated solutions in different vehicles, $K C_V$ remains constant, and this product is constant irrespective of the vehicle differences. If one assumes that no vehicle–skin interactions take place, and if the drug itself does not alter the skin in any way, then δ_S can be regarded as a constant. The drug's effective thermodynamic activity is proportional to the product of K and C_V, which, in fact, yields the drug's concentration at the surface of the skin. Any change in this product leads to a change in the tissue concentration that establishes the gradient across the skin.

To test the foregoing concept, two topical steroids were incorporated into a series of propylene glycol–water gels, and drug release into isopropyl myristate was studied (24). Drug solubility determinations were made for each system, and a receptor–vehicle phase partition coefficient was calculated. It was found that the maximum drug release occurred from gels containing the minimal amount of propylene glycol required to exactly dissolve all the drug. Excess propylene glycol required to exactly dissolve all the drug. Thus decreasing the thermodynamic activity of the drug and hence its release rate from the vehicle, is fully consistent with the foregoing argument. At the other extreme, when insufficient propylene glycol was available to completely dissolve the steroid, dissolution and intragel diffusion became part of the rate-limiting factors in the overall diffusion process over the multihour collection periods. The concept of using the thermodynamic activity of a drug in its vehicle as an indicator of its bioavailability from that vehicle was solidified in a subsequent series of studies by the group (25,26,54). For both fluocinonide and fluocinolone in propylene glycol–water gels, positive correlations were seen when data were compared from in vitro release, in vitro permeation, and in vivo vasoconstriction studies (26). The latter directly relate to concentrations of the steroids that build up