branes were used to separate the two phases, and it was assumed that the membrane contributed negligibly to the release resistance. Higuchi selected a diffusion coefficient (D) that yielded a best-fit curve for each set of data using the following modification of Eq. 6:

$$R = 200 \sqrt{\frac{Dt}{\pi h^2}} \qquad [25]$$

In this equation, R is the percentage of drug released, and h is the thickness of the ointment slab. The application of these theoretical equations to experimental data as a means of extracting diffusion coefficients from the data was significantly advanced by Spang-Brunner and Speiser (37). With the use of a dialysis cell method employing a cellulose ester membrane, the diffusion coefficients of resorcinol in various hydrogels were found to be on the order of 2.3 to 4.1 $\times$ 10^{-6} cm^2s^{-1}. Diffusion from ointments was found to be 50 to 300 times slower than diffusion from hydrogels. In yet another study, Koizumi and Higuchi (47) applied Eq. 25 to the measurement of the diffusion coefficient of pyridine from water–oil emulsions.

Subsets of the theoretical equations have been employed by Bottari et al. (40) and Di Colo et al. (39,41) in studies involving the release of drugs from gels and ointments across silicone rubber membranes. While investigating the release of salicylic acid as a function of concentration from emulsions (40), Eq. 6 was used to calculate diffusion coefficients in the emulsions. By plotting release rates against drug concentration for each ointment, the authors attempted to determine drug solubility by noting the concentration at which a deviation from linearity occurred. Reasonable agreement was claimed between these values and the independently obtained solubilities as determined visually. Through the use of Eq. 6, it was assumed that the membrane offered negligible resistance to diffusion of the salicylic acid. However, an appreciable lag time was observed in the mass versus square-root of time plots, thus indicating the possibility of membrane involvement in the release process during early times. Similar studies in which benzocaine was suspended in aqueous gels were performed by the same group (39). However, here, the membrane was assumed to offer resistance to diffusion, and Roseman and Higuchi's vehicle–boundary diffusion layer model was employed. In this instance, excellent agreement was found between the experimental data and theory.

Wahlgren et al. (48), in an interesting application of a standard solution to Fick's second law (7), calculated the diffusion coefficient of hydrocortisone in a lecithin–water lyotropic liquid crystalline solution. In this method, the diffusion coefficient was extracted