diffusional resistance offered by the membrane and be prepared to quantitatively account for it. This points to a fundamental flaw in many of the studies that have employed membranes, namely that the resistance offered by the membrane is ignored when analyzing the results. Although the assumption that this resistance is negligible may generally be safe when the formulation is applied as a very thick layer, nonetheless, without specifying values for K, D_m, and h_m, it does not seem possible that the experimental circumstances under which the assumption is valid can be assured.

Although the aforementioned experimental designs have been used frequently, there are several innate drawbacks in the designs that should cause one to exercise caution when attempting to interpret results (4). Although release of a drug from a vehicle occurs from thin vehicle films clinically, the vehicle is presented to the receiver as a relatively thick slab in most in vitro experiments. Release from such thick slabs is expected to assume an overall square root of time dependency, which might not occur if the vehicle were present as a thin film. This problem may be present in any type of release study involving a thick ointment application, regardless of whether or not a membrane is used. Another problem inherent in these studies is that experiments are usually conducted under closed conditions, which prevents the occurrence of compositional changes in the vehicle that might otherwise be manifest if the formulations were to be exposed to the atmosphere. In addition, the absence of a membrane could lead to solubilization of vehicle components by the solvent present in the receptor phase. The choice of a receptor phase itself creates problems, particularly if the phase is purported to be representative of the skin. For instance if one is studying the release characteristics of a steroid, isopropyl myristate might, in fact, be an appropriate choice for a receptor phase. However, for a small polar molecule, a phase with some capacity to dissolve the drug, perhaps water itself, might be a better choice.

B. Measurement of Diffusion Coefficients

Perhaps the first demonstration of the applicability of the theory concerning release of drugs from solution ointments was reported by Higuchi et al. (7). Using data that had been previously generated by Patel and co-workers (46), W. Higuchi was able to successfully apply a simplified version of the theoretical equation derived by T. Higuchi (Eqs. 5 and 6) to show that the kinetics of drug release from ointments do follow a square root of time pattern. The release experiments involved the liberation of radiolabeled iodine from hydrophilic ointments into a stirred aqueous reservoir. Visking mem-