when considering diffusion processes in a continuous medium. The formulation of these enhancers is not simple because they often interact with emollients and such, that are put into a cream and can be rendered ineffective. Because of potential irritation problems with enhancers, they are most practical for short-term use. For prolonged application, more attention will have to be placed on regulating cutaneous irritation.

III. EVALUATION OF VEHICLE PERFORMANCE

A. In Vitro Evaluation

As described in earlier sections one can use thermodynamics and elementary diffusion theory as guides for optimizing the flux. In the final analysis, however, one should measure the penetration of the drug from the actual vehicles. A variety of experimental methods (described elsewhere in this book) are available for determining cutaneous flux in vitro, and they are quite simple to use. These in vitro techniques are an invaluable guide to the formulation of topical dosage forms and should be a standard laboratory tool. Without a measurement of penetration, there is virtually no way to compare different dosage forms. When employing enhancers, it is absolutely necessary to make these measurements.

We prefer to use human skin, when possible, although animal skin is acceptable, to compare different formulations. Our experience has been that for comparing vehicles there is good correlation between human and animal skin, but sometimes animal skin will give a false-positive result when studying skin penetration enhancers. Although there are a number of diffusion apparatus available, we prefer the one shown in Figure 3 (12) because it is relatively inexpensive and occupies very little laboratory space.

Typical data from in vitro experiments are depicted in Figure 4 for penetration from large reservoir systems in which the effect of an enhancer is shown. Here, the effect of a lipid fluidizing agent is shown for the enhancement of lipophilic drugs (10). The lag time is an important factor to minimize for treatment of acute symptoms such as pruritis and burns. For treatment of less acute symptoms, this factor is of less importance. Although for transport across homogeneous membranes the lag time is only a function of the diffusion coefficient and not the partition coefficient, it is a function of partition coefficient for heterogeneous membranes (13). The lag time may not be well defined in the presence of enhancers, especially if the membrane barrier properties change over a reasonable time period. The enhancer, however, should shorten the onset time for pharmacologic response.

For drugs that penetrate rapidly, one can use a vehicle with a lower partition coefficient to sustain the delivery, rather than have