be the drug of choice. Once again, the balance between localized effect and systemic breakthrough is important.

The physicochemical characterization of a drug may not be completed early enough during drug development efforts to have both the partition coefficient and water solubility data available when evaluation by computational methods is desired. If partition coefficients are not available, then they can be calculated using various group contribution methods (8). Because these computational techniques are becoming more readily available commercially, they will not be further discussed here. High-performance liquid chromatography (HPLC) methods are also cited in the literature that correlate retention time to partition coefficients (22,23). These methods have the advantage that small amounts of the drug material are required to determine the partition coefficient. Thus, partition coefficients can be experimentally determined by HPLC when only a small quantity of the drug is available, or partiton coefficients can be calculated based upon drug structure alone.

Knowledge of the partition coefficient and melting point of crystalline compounds can be utilized to estimate the water solubility of the compound by use of the method of Valvani and Yalkowsky (9). Specific equations for various classes of organic compounds are given in Table 3. This water-solubility value combined with the calculated or experimental partition coefficient can then be utilized to predict flux values as shown previously. Table 4 gives predicted transdermal flux values for a series of benzodiazepines, calculated using partition coefficients and melting points (24). This is an example of how predicted flux values for a series of analogues can be combined with pharmacokinetic information (25) to select the drug candidate most likely to provide the most efficacious topical treatment. The use of these models for a series of timolol prodrugs (26) is given in Table 5. Because these compounds are expected to be metabolized to the same active species, the flux values are the primary concern. However, the rate of hydrolysis may also be important for localized delivery, since the prodrug could be "swept" by the targeted site of delivery before conversion to the desired species, if the rate of hydrolysis was sufficiently slow.

V. CONTOUR PLOTS

Although the models described in this chapter may prove useful in evaluating existing drugs for use as topicals, a more fundamental utility exists for these computational methods; namely, a set of qualitative guidelines can be established that will aid the synthetic chemist in designing drug analogues and prodrugs. In the past, vague guidelines existed indicating that increases in lipophilicity re-