treatment of retention as a function of pH, the reader is referred to the works of Lewis et al. (20) and Schoenmakers and Tijssen (21).

As stated in Table 1, it is important to know the salt form of the drug substance of interest or whether it is amphoteric. This information is invaluable to the development of the analytical methodology because it will aid in the optimization of the method to effect better separation, resolution, and chromatography. If the drug is amphoteric, the pH can be selected whereby the compound exists as a single species and not a mixture of species. Mixed species will lead to poor separations. On the other hand, if the drug has different salt forms, say the hydrochloride and the napsylate (e.g., *d*-propoxyphene hydrochloride, Darvon®, and *d*-propoxyphene napsylate, Darvon-N®, both drug products marketed by Eli Lilly), the problem is not as critical, for

The salts represent different products and are marketed separately for different pharmacokinetic effects, i.e., different absorption profiles, with the hydrochloride being more soluble, and thus showing a faster absorption and distribution.

In solution, both salts will be dissociated from the organic propoxyphene moiety so that the final analytical methodology is appropriate for the separation and detection (or titration) of the analyte free base. For example, in the USP monographs for the two propoxyphene (hydrochloride and napsylate salts) APIs and their several products (22), the final analytical methods, be they titrimetric or chromatographic, all detect the analyte free base propoxyphene, and the assay percentage is calculated using a molecular weight correction factor.

10.4. Role of Solvent Type

Solvent type (methanol, acetonitrile, and THF) will affect selectivity similarly for ionic and neutral analytes. Hence changing a solvent would be a useful variable in the separation. The choice between methanol and acetonitrile may be dependent on the solubility of the analyte as well as the buffer used. While THF may be the least polar of the three, it has the highest solvent strength. If that property is not essential, its odor and potential peroxide formation may be a deterrent.

10.5. Role of Mobile Phase

The mobile phase composition (percent aqueous to organic) as well as the solvent strength will affect both α (solvent selectivity) and k' (solvent strength). The sample solvent will have a similar effect as well and may lead to peak distortion if the polarity between the mobile phase and the sample solvent is great. Thus, if at all possible, it is best to dissolve the sample in the mobile phase, if not, at least to make the final dilution in the mobile phase.

Chromatographic separations thus vary with solvent properties and are related to sample solubility, polarity, and solvent strength. Solvents that interact strongly with the sample will increase the sample solubility and decrease the chromatographic retention as more sample ions exist in the solvent and are not able to be in equilibrium with the adsorbent surface. Thus changing the organic solvent will change the selectivity. Polarity is the summation of dipole and hydrogen bonding