



FIGURE 2 Effect of relative permittivity (E_r) on the solution degradation rate constant for trecetilide fumarate, a compound undergoing SN_1 substitution and E_1 elimination through the same carbonium ion intermediate.

being able to scale up the manufacturing process while maintaining tight control of the level of degradation. The rate constant (k) for drug degradation was decreased substantially as the *tert*-butanol content was increased. The work required to separate two charges to infinite distance is related to the function $(1 - 1/E_r)$ where E_r is the relative permittivity of the medium. The linear relationship observed between $\log k$ and this function (Fig. 2) indicates that the decreased relative permittivity of the solvent system (i.e., the increased work required to remove the fluoride group) was the major effect for the improved solution state stability of trecetilide fumarate. The decreased ability of *tert*-butanol (relative to water) to solvate and stabilize the two ions appeared to be less of a factor. The use of *tert*-butanol allowed formulation and filling on a production scale over a 24-hour period for this compound. The resulting freeze-dried product was predicted to have an acceptable shelf life of at least two years at ambient temperature. This was a dramatic improvement compared with a frozen aqueous solution that had to be stored at -80°C and required use within three hours of thawing and admixture preparation. This type of effect would be expected to be observed for many other drug products that are degraded in the presence of water.

IMPACT ON THE FREEZE-DRYING PROCESS

Effect on Freezing

The first stage of freeze-drying involves freezing the solution to remove solvent (typically water) from the drug and excipients through the formation of ice. The resulting semi-frozen system is cooled further to transform all components into a frozen state. A selected time-temperature profile is achieved by placing the solution, which is commonly held in glass vials or syringes, onto cooled shelves.