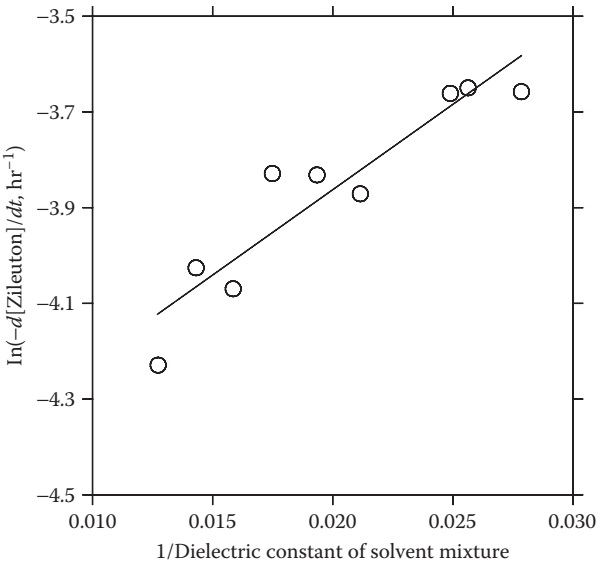

FIGURE 9.3 Effect of dielectric constant of water–ethanol–propylene glycol mixtures on the observed rate constant for zileuton.

Since the degradation of zileuton follows a hydrolytic degradation in aqueous environment, the increase in the rate of degradation in nonaqueous system (e.g., 50:50 ethanol:propylene glycol mixture exhibited the highest rate) was attributed to the solvent participation in the degradation mechanism, often referred as solvolysis. Patel et al. (1992) have reported that for their Drug 1 containing a carboxylic acid functional group, as compared to an aqueous medium, an increase in the rate of degradation was observed for the glycerin-containing medium.

COSOLVENTS IN ORAL COMMERCIAL PRODUCTS

Approximately 50% of the commercially available products are delivered through oral route. The majority of these products are formulated as either tablets or capsules. However, there is a significant amount of products still formulated as solutions, syrups, and elixirs. The primary role of the liquid dosage form is for pediatric and geriatric population who can swallow tablet or a capsule. In addition, solubilized formulations help overcome dissolution rate limited absorption issue. For an example, water-insoluble Digoxin when formulated with propylene glycol, ethanol with other excipients in Lanoxin Elixir, 70%–85% bioavailability is observed as a solubilized dosage (*Physician's Desk Reference* 2006). The solubilized formulations are also delivered through soft or hard gelatin capsules. In addition to solubilization, these capsule dosage forms have additional challenges such as cross-linking and compatibility. These are discussed in a separate chapter in this book and are not discussed further in this chapter.

A quick survey of the literature and pharmaceutical development report (PDR) suggests that the *most* commonly used water miscible cosolvents are dimethylacetamide (DMA), dimethyl sulfoxide (DMSO), ethanol, glycerin, polyethylene Glycol 300 and 400 (PEG), propylene glycol (PG), hydroxyl propyl-β-cyclodextrin (HP-β-CD), sulfobutyl-β-cyclodextrin (Captisol®), as well as surfactants such as Cremophor® (EL&RH), polysorbates (Tween® 20 and 80), *d*-∞-tocopheryl polyethylene glycol succinate (TPGS), Labrasol®, Labrafil®, Gellucire®, and Solutol HS 15®. Although, many of these surfactants at or above their critical micelle concentration (CMC) will self-assemble into micelles and may enhance solubilization process.

Table 9.1 is an alphabetical listing of commercially available solubilized formulations.