For any compound marketed by a pharmaceutical concern, at one time during its development, there should be a concerted project to establish a very exact pH profile. To do this correctly is a time-consuming undertaking. However, the information that can be gleaned from it is very important with regard to formulations, and it is therefore customary to carry out an approximate kinetic pH profile (Carstensen et al., 1992) early in the development stage. This will allow formulation of solutions for injections and for oral products as well, at a pH, and using buffers, that will give the best stability. Without it formulation is essentially guesswork.

11. LIQUID COMPATIBILITIES

The pH profile is the most important part of liquid compatibilities. However, two component systems are set up in aqueous (or other types of) solutions and treated as in Section 10 of Chapter 12. This is now required in the stability guidelines, which state that "it is suggested that the following conditions ... be evaluated in studies on solutions or suspensions of bulk drug substances: acidic and alkaline pH, high oxygen and nitrogen atmospheres, and the presence of added substances, such as chelating agents and stabilizers" and it is suggested "that stress testing conditions ... include variable temperature (e.g., 5, 50, 75°C)."

11.1. Aqueous Solution Compatibility

In general, such studies are carried out by placing the drug in a solution of the additive. These can be (and usually are) a heavy metal (with or without chelating agents present) or an antioxidant (in either oxygen or nitrogen atmosphere). Usually, both flint and amber vials are used, and in many cases an autoclaved condition is included. This will answer questions about susceptibility to oxidation, to light exposure, and to heavy metals. These are important questions as far as injectable compatibilities are concerned. Exposure to various plugs is frequently included at this point so that early injectable preparations can be formulated.

For preparations for oral use, knowledge of the desired dosage form is important, but compatibility studies with ethanol, glycerin, sucrose, corn syrup, preservatives, and buffers are usually carried out. This type of study also gives an idea of the activation energy, E, of the predominant reaction in solution. Arrhenius plots for compounds in solution are usually quite precise.

11.2. Nonaqueous Liquids

With transdermal dosage forms being of great importance of late, it is advisable to test for compatibilities with "ointment" excipients and with polymers (e.g., ethylvinyl polymer, if that is the desired barrier). In the case of transdermals, the dosage form is either directly placed in a stirred liquid or it is placed in a cell with an appropriate membrane (e.g., Cadaver skin) to estimate the release characteristics of the drug from the ointment (Chien et al., 1983).

It should be noted here that if the overall flux is J, then

$$\frac{1}{J} = \frac{1}{J_{\text{ointment}}} + \frac{1}{J_{\text{membrane}}} \tag{9.31}$$