with a high negative zeta potential do not show any change in their particle-size distribution after autoclaving. Emulsions with a lower negative value, on the other hand, would generally separate into two phases during autoclaving. Because the stability of phospholipid-stabilized emulsions is dependent on the surface charge, these emulsions are normally autoclaved at pH 8–9.

7.4.1 Stability Considerations

Newer drug molecules appear to be more reactive and potent in their response. As a result, they are also more reactive in the dosage forms, and when the dosage forms are liquids, the stability becomes a serious challenge to overcome. This is one reason why solid dosage forms are preferred by formulation scientists. A basic matrix to evaluate stability potential can take scores of permutations and combinations of pH, ionic strength, dielectric constant, temperature, and the like. Given the small quantity of substance available at the preformulation stage, it is unlikely to complete these studies with sufficient vigor.

The degradation kinetics of drugs in solution state has been a broad subject dealt with in major textbooks and in a large number of detailed review articles. What needs to be understood at the preformulation level are gross observations as to whether a drug would sustain the solution or liquid environment for any significant length of time. Quick pH and accelerated testing is required, where the quantity of the substance available is sufficient for the purpose. At this stage, stability may be tested with most likely cosolvents, particularly those used in pediatric or geriatric dosage forms.

For parenteral formulations, sterility can be maintained either by sterile filtration or by autoclaving. It is noteworthy that there is no history of any significant recalls of products that were autoclaved, and thus, manufacturers prefer to use this method of sterilization, where possible; obviously, it cannot be used where drugs are inherently unstable to heat, such as the biological products. Autoclaving (usually 15–20 minutes at 121°C) at various pH values is a good test to study the impact on impurities, color, pH, and other degradation products. The autoclave cycle should ideally represent a real-time manufacturing process, with its common fill, heat-up, peak-dwell, and cool-down steps.

7.4.2 Oxidation

Oxygen sensitivity is common for many molecules. Oxidation reactions are the most difficult reactions to understand, let alone prevent. As a result, oxidation-prone compounds are combined with antioxidants. In a solution form, the degradation is fast, particularly in the presence of trace metals.

The common antioxidants, such as water-soluble sodium bisulfate, sodium sulfite, sodium metabisulfite, sodium thiosulfate, sodium formaldehyde sulfoxylate, L- and D-ascorbic acid, acetylcysteine, cysteine, thioglycerol, thioglycollic acid, thiolactic acid, thiourea, dithithreitol or oil-soluble propyl gallate, butylated hydroxyanisole, butylated hydroxytoluene, ascorbyl palmitate, nordihydroguaiaretic acid, and *a*-tocopherol are widely used in pharmaceutical formulations. Oxygen-sensitive substances should be screened for their compatibility with a range of antioxidants. One of the most commonly used antioxidants is metabisulfite. It should be noted that bisulfite