Pharmaceutical Excipients, 1994). It should be noted that ascorbic acid derived oxygen scavengers are also reducing agents, and in fact can promote rather than retard peroxidation if metal ions are present (Sevanian and Ursini, 2000); inclusion of a chelating agent such as ethylene diamine tetraacetic acid (EDTA) in the formulation will prevent this and enhance the antioxidant activity of ascorbates. Use of ascorbates with drugs sensitive to reducing agents should be avoided. Use of a nitrogen atmosphere for formulation manufacture is another, but less convenient, method for excluding oxygen.

Hydrolysis is the other important mechanism for some lipids (glycerides and phosphoglycerides) to degrade. Lowering of pH can arise from both hydrolysis and lipid peroxidation (Arakane et al., 1995), as both processes can give acid products. It has also been reported that hydrolysis and peroxidation can act in synergy with one another in liposome bilayers (Swern, 1995), but it is uncertain whether this can happen for other structures since different mechanisms are operative for emulsified lipids and bulk lipids (Antolovich et al., 2002). Hydrolytic products (e.g., free fatty acids, mono- and diglycerides, and lyso-phospholipids) can form that can alter the surface properties and zeta potential of the emulsion and distribute into the aqueous phase (Herman and Groves, 1992, 1993). Fatty acid formation can also decrease the pH and increase the conductivity of the emulsion (Santos-Magalhaes et al., 1991). Hence, these two parameters should be monitored to aid stability evaluation. The emulsion excipients (namely, oils, surfactants, and cosolvents) should be monitored by periodic assays to insure no loss of excipient concentration.

Physical stability. As indicated earlier, conventional emulsions are inherently unstable from a physical standpoint. Poor physical stability is ultimately exhibited by phase separation, which can be visually monitored. Certain properties of the emulsion will start to change long before this separation is visually apparent. An increase in particle size is particularly indicative of physical instability, since this monitors the coalescence or flocculation that is part of the process involved in ultimate phase separation. Increases in viscosity (due to flocculation) and changes in zeta potential (arising from a decrease in droplet surface area) are both indicative of poor physical stability. The presence of drug and cosolvents can potentially hasten the phase separation.

From a theoretical standpoint, physical stability is probably the most complex property of emulsions. The key factor in determining the stability of an emulsion is believed to be the interfacial tension between the two phases, and lower interfacial tension (primarily governed by the surfactant) will increase the stability (Collins-Gold et al., 1990). Very low interfacial tension is thought to be the primary factor leading to the stability of microemulsions. A number of models allowing prediction of the stability of emulsions have been put forth. One of the most useful approaches is the so-called DLVO theory, developed over 50 years ago by Derjaguin and Landau (1941) and Verwey and Overbeek (1948). According to this theory, the stability of an emulsion depends on a balance of electrostatic repulsive forces and London-type Van der Waals attractive forces. Thus, higher surface charge (characterized by high absolute values of the zeta potential) will generally tend to stabilize emulsions due to the higher repulsion of the droplets from one another. For example, a 70% PC emulsion had a higher overall physical stability than a 99% PC emulsion, reflecting the latter's lower surface charge (Yamaguchi et al., 1995). An overabundance of electrolytes will generally tend to destabilize emulsions due to a lowering of the surface charge, leading to a so-called salting out effect, wherein the emulsion will undergo flocculation and phase separation at sufficiently high electrolyte concentration. Calcium and other divalent ions are particularly destabilizing. A parameter can be derived known as the *critical flocculation concentration* (CFC), which is the electrolyte concentration at which flocculation begins. For the PC emulsions described earlier, the CFC's for $CaCl_2$ were 0.4 mM for 99% PC and 1.2 mM for 70% PC (Yamaguchi et al., 1995).