cholesterol contents [230]. The authors suggested that increased peroxidation at 10 mol% cholesterol could be attributed to the coexistence of liquid disordered (LD) and liquid ordered (LO) phases.

Incorporation of Charged Lipids

The interest in the effect of the inclusion of cationic or anionic lipids in a liposomal formulation is often driven by use of cationic lipids such as 1,2-Dioleoyl-3-trimethylammonium-propane (DOTAP) in lipid-based nucleic acid delivery vehicles or the desire to better understand the peroxidation of biomembranes which are inherently negatively charged. A significant amount of research has been conducted to assess the effect of the inclusion of cationic or anionic lipids in liposomal formulations on iron-catalyzed lipid peroxidation. Some studies have concluded that the inclusion of anionic lipids, in particular 1,2-dipalmitoyl-sn-glycero-3-phospho-L-serine (DPPS), inhibits lipid peroxidation due to binding of the cationic iron ions by the negatively charged headgroup, thereby preventing the iron-catalyzed decomposition of lipid hydroperoxides [231, 232]. Conversely, Kunimoto et al. [210] found that anionic liposomes readily underwent peroxidation, whereas neutral and cationic liposomes were not as prone to oxidative degradation. The increased peroxidation of anionic liposomes was attributed to increased binding with iron or the close proximity of the ferrous ions and the surface of the bilayer. In many studies, there was either a slight or a negligible effect of liposome charge on liposomal peroxidation initiated by azo compounds [231–233].

Incorporation of Antioxidants

The addition of antioxidants to liposomal formulations is a common strategy which is used to slow or, in some cases, inhibit the oxidative degradation of susceptible liposome components (e.g., polyunsaturated lipids). Antioxidants are typically characterized as either hydrophilic and water soluble (e.g., ascorbic acid, uric acid) or lipophilic (e.g., α-tocopherol, 2,2,5,7,8-pentamethyl-6-chromanol, PMC). Noguchi et al. [222] examined the peroxidation of both methyl linoleate micelles and PC liposomes in the presence of AAPH (water soluble) or 2,2'-azobis(4-methoxy-2,4-dimethylvaleronitrile (Meo_AMVN, lipophilic). Methyl linoleate micelle oxidation was followed by measuring the formation of hydroperoxides and the consumption of oxygen. The oxidation of methyl linoleate in the presence of MeO–AMVN was inhibited by PMC but not by ascorbic acid. In the presence of AAPH, methyl linoleate oxidation was inhibited by ascorbic acid. Not surprisingly, methyl linoleate oxidation was inhibited effectively when the antioxidant and the source of the radicals (i.e., the azo initiator) were together in either the aqueous solution or the lipid bilayer. When the MeO–AMVN (lipophilic) and ascorbic acid (water soluble) were added to methyl linoleate samples, oxidation was only inhibited when a cationic surfactant, tetradecyltrimethylammonium bromide (TTAB), was also present. It was proposed