

in the fatty acid tail of the lipid. The carbon–hydrogen bond energy is decreased for allylic (88 kcal/mol) and bisallylic (75–80 kcal/mol) carbon–hydrogen bonds relative to alkyl carbon–hydrogen bonds (101 kcal/mol; Fig. 1) [207]. The decreased bond energy as well as the resonance stabilization of the resulting lipid radical underlies the greater propensity of lipids containing two or more unsaturated sites to undergo peroxidation [206, 208]. During propagation, the reaction of molecular oxygen with a lipid radical results in the formation of peroxy radicals [208]. Once formed, the peroxy radical can then abstract a hydrogen atom from another lipid molecule leading to the formation of hydroperoxides and lipid radicals [208]. In addition to these reactions, a number of other reactions such as fragmentation, rearrangement, and cyclization can also occur [208]. Termination, the final step of lipid peroxidation, occurs when nonradical products are formed as a result of the coupling of two radicals. It has been demonstrated that peroxidation can affect the physical properties (i.e., permeability and fluidity) of liposome bilayers [209–211]. Besides peroxidation, hydrolytic degradation of lipids is also of concern. The ester functionality which connects the glycerol backbone with the fatty acid tails is susceptible to hydrolysis and results in the formation of free fatty acids, lysophospholipids, and glycerophospho compounds [212]. Hydrolytic degradation can impact liposome size, rigidity, and drug entrapment [213]. Due to the limited stability of aqueous liposomal formulations, these formulations are often lyophilized. Little is known about the chemical stability of lyophilized liposomal formulations (i.e., lipids in the dried state). Predominately, the studies which have investigated lipid stability have focused on aqueous liposomal formulations. However, liposomal leakage and the retention of small molecules have been studied in lyophilized and aqueous formulations [107, 214, 215]. To better understand how to maximize the stability of lipids in the dried state, it is necessary to review the studies which have investigated the chemical stability of lipids in aqueous formulations. The continued development of lipid-based therapeutics necessitates the further investigation of the stability of lyophilized liposomal formulations.

Oxidation

In the studies which have examined the stability of liposomal formulations, typically, transition metal ($\text{Fe}^{2+}/\text{Fe}^{3+}$) catalysts or azo compounds are utilized to facilitate the initiation of lipid peroxidation. The various ways that transition metals can affect lipid peroxidation has been studied extensively, and several possibilities have been proposed. The reaction of iron with oxygen and/or hydrogen peroxide via the Haber–Weiss and/or the Fenton reactions results in hydroxyl radical formation which can then serve as the initiator free radical [216, 217]. It is well known that the direct reaction of oxygen with lipid molecules is spin forbidden due to the electronic configuration of these molecules [218]. Iron has also been suggested to mitigate the spin restriction of oxygen and increase the rates of oxidation of biological molecules (e.g., lipids) by serving as a bridge [219]. Another route by which iron can affect lipid peroxidation is through direct initiation. Direct initiation of lipid