Polymerized and Fluorinated Liposomes

Early in the development of liposomes, it was recognized that their plasma instability could be a serious detriment in certain applications. Consequently, there were efforts to first incorporate polymerizable lipids into the liposomal bilayers, and then initiate polymerization by, for example, photolysis, to form interchain crosslinks to stabilize the bilayer. The most commonly used polymerizable lipids have been PCs-containing diacetylene or butadiene moieties in the tailgroups (Hupfer et al., 1983; Freeman et al., 1987). The permeability of polymeric liposomes to the water-soluble marker 6-carboxy flourescein was substantially decreased and resistance to organic solvents and detergents was increased relative to nonpolymeric liposomes (Hupfer et al., 1983). Recently, pH-sensitive polymeric liposomes containing ampicillin were prepared using polydiacetylene lipids at neutral pH 7; under acidic conditions, drug is released rapidly (Won et al., 2013) Polymerized liposomes have not been used clinically, perhaps owing to concern for the potential toxicity of the polymerizable lipids. Use of polymeric liposomes in solubilization of water-insoluble drugs would probably have limited value, since in this case partitioning from the bilayer is of greater importance than *trans*bilayer permeability. Stability of drugs located in the lipid bilayer under the polymerization conditions would also be of serious concern.

A related technology is the use of fluorinated vesicles, composed of an amphiphile with a fluorocarbon rather than hydrocarbon tail group. Fluorocarbon chains tend to be more hydrophobic and more rigid than the hydrocarbon chains, providing a driving force for fluorinated amphiphiles to self-organize into lamellar systems that are better organized and more stable than the corresponding hydrocarbon systems (Riess, 1994). This results in a significant decrease in permeability for fluorinated vesicles, both in buffer and in human serum. For example, there was a 100-fold reduction of 6-carboxyfluorescein permeability coefficient at 75°C for DMPC liposomes when the myristoyl groups were replaced with $C_6F_{13}C_6H_{12}CO-$ groups, or a 2000-fold reduction when replaced with $C_8F_{17}C_4H_8CO-$ groups (Riess, 1994). For DSPC liposomes, there was a 10-fold reduction in 6-carboxyfluorescein permeability coefficient in buffer at 75°C when stearoyl groups were replaced with $C_6F_{13}C_{10}H_{20}CO-$ groups. This change resulted in improved serum stability at 37°C, with the DSPC and fluorinated vesicles showing 40% versus 15% loss of entrapped marker after 28 h, respectively, as well as up to a 13-fold increase in circulating half-life (Riess, 1994). Similarly, fluorinated liposomes were shown to be more resistant to the lytic action of detergents compared to conventional DSPC liposomes (Gadras et al., 1999). Fluorinated vesicles have the advantage over polymerized liposomes in that conventional methods for preparation can be used, without use of photoactivation. The fluorinated bilayer does not prevent the use of remote-loading techniques for vesicle preparation, as has been shown for encapsulation of doxorubicin into fluorinated vesicles (Frezard et al., 1994). Fluorinated vesicles have not been used clinically, perhaps owing to unknown toxicity.

Long-Circulating Sterically Stabilized Liposomes

Recently there has been a great deal of interest in liposomes whose surfaces have been derivatized or modified to prolong their circulating lifetime. There have been several approaches to this modification: the earliest utilized incorporation of sialic acids (e.g., ganglioside GM1) into the bilayer (Allen and Chonn, 1987; Gabizon and Papahadjopoulos, 1988; Allen et al., 1989). More recently, polyethylene glycol (PEG)-derivatized liposomes, normally prepared by incorporating 10–20 mol% of PE to which PEG has been covalently attached at the amino group of PE, have become the method of choice for preparing long-circulating (*Stealth*) liposomes (Woodle, 1993). The surface modification can increase the circulating half-life from 2 to 3 h for conventional liposomes to over 24 h for sterically stabilized liposomes (SSL) owing to reduced RES uptake. For example, an 18-fold increase in half-life was observed when PEG lipid was included in small