solutes (such as glucose) and higher molecular weight compounds generally pass very slowly across intact phospholipid bilayers. Diffusion across the bilayer is quite rapid for smaller molecules of neutral charge (e.g., water and urea), and somewhat slower for protons and hydroxyl ions. Sodium and potassium ions traverse the membrane very slowly. Gel-phase bilayers are less permeable than the corresponding fluid bilayers, that is, increasing the temperature above T_m will increase the permeability.

Phospholipid packing can also affect bilayer permeability. At the membrane boundary, where the lipid compartment interfaces with the bulk aqueous phase, the limited rotational and translational freedom normally manifests itself in alignment of lipids in a regular two-dimensional array with molecules all adopting a set distance and orientation with respect to each other. However, packing abnormalities (point defects, line defects, and grain boundaries) can occur as a result of impurities resulting from an altered configuration or change in conformation of the acyl chain carbons from trans to gauche. Packing abnormalities thus lead to small exposed areas of the membrane, which facilitate the passage of small molecules through that area of the bilayer, increasing the permeability.

When considering hydrophobic drugs that are localized primarily in the lipid tail-group region of the bilayer, the more important parameter is the partition coefficient of drug between lipid bilayer and aqueous phase. One of the main goals of formulation development would be to maximize this number. Partition coefficient is a static parameter, whereas rate of efflux from the bilayer would be the corresponding kinetic parameter, analogous to the permeability parameter of water-soluble molecules.

Properties of Negatively Charged Phospholipids

In negatively charged phospholipids, three possible forces, namely, steric hindrance, hydrogen-bonding, and electrostatic charge, regulate headgroup interactions of the bilayer. For example, dipalmitoyl phosphatidyl glycerol (DPPG), with its bulky glycerol group and electrostatic repulsion of the deprotonated phosphate at pH 7, has a phase transition temperature about 10°C below that of DPPC. In contrast, DPPA, with a small headgroup and negative charge at neutral pH (leading to hydrogen-bonding), has a higher relative main transition temperature. Another factor is a pH effect: at high and low pH, the T_m is brought down, particularly at high pH, where electrostatic repulsion can push the headgroup apart. Similarly, acidic phospholipids can bind strongly to divalent cations (Ca^{2+}, Mg^{2+}), which will decrease the electrostatic charge of the headgroups, condense the bilayer (i.e., increase the packing density in the gel phase), and thus increase the T_m. Therefore, at the appropriate ambient temperature, the addition of cations can induce a phase change from liquid crystalline to gel phase.

Properties of Cholesterol-Containing Lipid Bilayers

Sterols are important components of most natural membranes, with cholesterol and its derivatives being the most important and predominant sterol in animal tissues. Incorporation of sterols into liposome bilayers can bring about major changes in the properties of these membranes. Cholesterol does not form bilayer structures by itself, but having some degree of amphipathic nature, it can be incorporated into phospholipid membranes at very high concentrations (up to 2:1 molar ratios of cholesterol to PC). While it will generally have little effect on the actual phase transition temperature, it can broaden the transition of the bilayer considerably, and in some cases can completely abolish the heat of transition. In the presence of cholesterol, the freedom of molecular motion of the bilayer above the phase transition is decreased, but below the phase transition, mobility is increased. Thus, the overall effect of cholesterol is to moderate the differences between gel and liquid crystalline phases. A corollary to this is that cholesterol will not only fluidize bilayers containing saturated phospholipids, but also will increase the fluidity of bilayers containing unsaturated phospholipids. Some of the benefits that may result from use of cholesterol in a liposomal formulation are decreased permeability of the bilayer, smaller and more uniform size distribution, and prevention