INTRODUCTION

History of Liposomes

Over 40 years ago, Alec D. Bangham, a British physician, investigated the relation of cell membranes to phospholipid molecules and discovered phospholipid vesicles, which he initially called smectic mesophases or *tiny fat bubbles*, and later named liposomes. He demonstrated that in water these phospholipid molecules arrange themselves spontaneously into bilayer structures, so that the hydrophobic tails are shielded from the water by hydrophilic heads (Bangham et al., 1965, 1992). Since then, liposomes have been extensively investigated by scientists from many disciplines. The enthusiasm for liposome research had by 1989 resulted in the publication of more than 20,000 scientific articles on liposomes in fields as diverse as gene transfer and nutrition (Ostro and Cullis, 1989); since that time, this number has more than doubled. In addition, more than 1000 patents have been issued or were filed dealing with specific aspects of liposomes (Crommelin and Schreier, 1994). However, early research interests in liposomes were limited primarily to physiologists and biophysicists. The physiologists used liposomes as models to investigate ionic flow across cell membranes, and the biophysicists used them to study the phase behavior of lipids under precisely controlled conditions (Ostro and Cullis, 1989). Later on, biopharmaceutical scientists started to utilize liposomes as delivery or targeting systems for many drug substances (Ostro, 1992; Sharma and Sharma, 1997). More recently, pharmaceutical formulation scientists found that liposomal delivery is an exciting technique and particularly useful to deliver water-insoluble compounds (Chen et al., 1986; Lidgate et al., 1988; Tasset et al., 1992). Many drugs such as anticancer and anti-HIV compounds are water insoluble, and the proportion of new drug candidates that are water insoluble has increased dramatically. The lipophilic phase of the lipid bilayer membrane affords a useful environment to dissolve lipid-soluble compounds. Hence, liposomal delivery offers the possibility of formulating highly promising but water-insoluble compounds that otherwise could not be developed for medical uses because of solubility problems in aqueous solution (Vries et al., 1996; Sharma and Sharma, 1997).

In Vivo Behavior of Liposomes

A variety of routes, including intravenous (IV), intramuscular (IM), and subcutaneous (SC) are used to introduce liposomes into a human body; however, IV injection is the most common and effective means. On injection, liposomes interact with at least two groups of plasma proteins (namely, lipoproteins, and opsonins), and cells in blood. Depending on the liposome composition, lipoproteins can attack and degrade liposomes by removing phospholipid molecules from the lipid bilayer structure. This leads to the destabilization of the bilayers of vesicles, leading to release of the entrapped drug molecules into the blood circulation. Opsonins adsorb onto the surface of the vesicles; the resulting opsonin–liposome complexes, along with the entrapped drug, fall prey to the phagocyte cells of the reticuloendothelial system (RES) (Gregoriadis, 1990).

Of the postulated mechanisms by which liposomes can interact with cells of the RES, adsorption, endocytosis, lipid exchange, and fusion are believed to be the most important (Figure 14.1) (Ostro, 1987).

In the mechanism of adsorption, liposomes can be adsorbed onto the membrane of any cell under suitable conditions, for example, by electrostatic attraction. During liposome–cell adsorption, the