the headgroup region of the phospholipid and retain the bilayer in a liquid crystalline phase in the dry state (Crowe and Crowe, 1992). If one decides to use lyophilization and storage in the dry state to extend the shelf life of a liposomal formulation, one should monitor liposome size, lamellarity, encapsulation efficiency, drug potency, and other parameters both before and after lyophilization and reconstitution. Such a protocol was followed for a liposomal hemoglobin formulation containing trehalose, proposed as a blood substitute (Cliff et al., 1992).

PHARMACEUTICAL APPLICATIONS

The delivery of water-insoluble drugs into the target sites in the human body has always been a challenge, because these compounds have low solubilities and will precipitate out in an aqueous environment. Liposomes, as one of the latest new drug delivery systems, efficiently meet this challenge. Compared with other solubilization techniques for water-insoluble drugs, liposome technology is a superior choice in many cases. In a study conducted by van Bloois et al. (1987), the improvement of the apparent solubility of almitrine bismesylate, a poorly water-soluble lipophilic compound was compared among three techniques: liposomes, mixed micelles, and oil-in-water (o/w) emulsions. Liposomes possessed superior properties with respect to almitrine solubilization and stability compared with the other two types of formulations. A 100-fold increase in apparent almitrine solubility relative to the aqueous buffer could be achieved. In addition to their function of solubilizing the water-insoluble drugs, liposomes as drug delivery systems can change the biodistribution of a drug and thereby alter its therapeutic index. Hence, liposome technology has been successfully used to formulate water-insoluble pharmaceutical agents. Examples of water-insoluble drugs that have been examined in liposomal formulations include annamycin, vincristine, mitoxantrone, and ciprofloxacin. The cancer therapeutic agent camptothecin and its analogs are also particularly challenging to formulate due to their poor water solubility and toxic effects. Hence, liposomal formulations have been evaluated for a number of camptothecin analogs, for example, topotecan, lurtotecan, 9-nitrocamptothecin, irinotecan, gimatecan (Pantazis et al., 2003; Stano et al., 2004; Castor 2005; Glaberman et al., 2005; Zamboni 2005). Four other examples are discussed more fully in the following section.

Amphotericin B

Amphotericin B, a polyene macrolide antibiotic, is a broad-spectrum antifungal agent for the treatment of systematic fungal infections (Gold et al., 1955; Gallis et al., 1990; Lyman and Walsh, 1992). It has remained the drug of choice for life-threatening invasive fungal infections over the past 30 years. Amphotericin B is practically water insoluble at pH 6–7, while at pH 2 or 11 in water it is very slightly soluble (ca. 0.1 mg/mL). The mechanism of pharmacological effect of amphotericin B is well established. This macrolide primarily binds with ergosterol, a common sterol in fungal membrane. Reaction with ergosterol produces pores in the cell membrane, allowing salts and other small molecules to escape the fungal cell. This action is fungicidal, a significant advantage in antifungal chemotherapy (Palacios and Serrano, 1978; Kerridge, 1986). However, amphotericin B also has toxic effects due to the binding with other sterols, including cholesterol, a common sterol in mammalian membranes (Medoff and Kobayashi, 1980). This leads to a range of serious side effects such as chills, fever, headache, nausea, azotemia, hypolalemia, hypomagnesemia, nephrotoxicity, and thrombophlebitis at the infusion site with associated local tissue damage. As a result, the usefulness of amphotericin B has been limited by its narrow therapeutic index. To increase its therapeutic index and reduce its toxic effects, liposomal formulations of amphotericin B have been investigated since 1981 (Adler-Moore, 1994). This polyene antibiotic can be incorporated into the lipid bilayer owing to its high lipophilicity (Hiemenz and Walsh, 1996).

Three lipid formulations of amphotericin B are now either marketed for clinical use or undergoing further study before they can be approved in various countries worldwide (Hiemenz and Walsh, 1996).