Amphotericin B or Amphotericin–phospholipid complex have already been approved. Plaux® (Lipoalprostadil), a cardiovascular and an anti-diabetic drug incorporated in liposome formulation, was launched in Japan in 1988. The use of liposomes as drug carriers for chemotherapeutic agents or biologic response modifiers has been actively pursued by several companies. DOXIL®, a liposomal formulation of doxorubicin developed by Sequus Pharmaceuticals (now Alza, part of Johnson and Johnson) was approved by the United States in 1995. DOXIL, one of the most successful liposome products, uses polyethylene glycol to increase circulation time, as discussed later. Myocet® is a non-pegylated liposomal doxorubicin product marketed in Europe. A liposomal formulation of muramyl tripeptide phosphatidylethanolamine, an immunomodulator, is marketed in Europe and has been submitted for a new drug application (NDA) in the United States. Other formulations, such as a topical formulation of minoxidil, a dermatological agent from Taisho developed by Upjohn, were launched worldwide in 1986. Iodinated liposome, a diagnostics from Sequus Pharmaceuticals (now Alza) is currently in use. Verteporfin is a photodynamic therapy agent developed by QLT Phototherapeutics. It was originally tested as an anticancer agent and is now marketed as Visudyne®, a treatment for age-related macular degeneration. Daunorubicin, cytarabine, morphine sulfate, and vincristine are other drugs that have come to the market as liposomal formulations (Table 14.1). Liposomal delivery of paclitaxel has been studied in a number of clinical trials for cancer, as have the chemotherapeutic agents docataxol, irinotecan, lurtotecan, topotecan, and cis-platin, with promising results. Besides those listed in Table 14.2, liposomal drugs that have been examined in clinical trials include mitoxantrone (Yang et al., 2014), lactoferrin (Ishikado et al., 2004), and tretinoin (Bernstein et al., 2002). Antisense oligonucleotides such as LEP-rafAON (Dritschilo et al., 2006), and siRNA (Schultheis et al., 2014) have been studied clinically. Liposomal combination therapies (Combiplex®) such as irinotecan:floxuridine and cytarabine:daunorubicin have been explored by Celator Pharmaceuticals. Besides injectables, nebulized liposomal formulations have shown some advantages in drug delivery to the lungs. For example, Amphotericin B (Monforte et al., 2009), cis-platin (Wittgen et al., 2007), and camptothecin (Verschraegen et al., 2004) have been examined clinically in nebulized liposomal formulations. Similarly, since there is evidence that liposomes and/or their components enhance penetration of drugs into the skin (Cevc, 2004), topical liposomal formulations of dithranol (Saraswat et al., 2007), superoxide dismutase (Riedl et al., 2005), idoxuridine (Seth et al., 2004), tretinoin (Patel et al., 2001), and heparin (Górski et al., 2005) have been tested in the clinic. Since 1990, there have been more than a dozen liposome projects in phase III/New Drug Application (NDA) stages, and numerous in phase I and phase II clinical studies. As of 2014, there were at least 107 active clinical trials containing the terms *liposome* listed by the Food and Drug Administration (FDA) (Kraft et al., 2014).

LIPIDS AND LIPID BILAYERS CLASSIFICATION OF LIPIDS

Phospholipids are found in all living cells and typically constitute about half the mass of animal cell plasma membranes (Cevc, 1992). The reason for the variety of membrane lipids might simply be that these amphiphilic structures have in common the ability to arrange as bilayers in an aqueous environment (Paltauf and Hermetter, 1990). Thus, the use of endogenous phospholipids to form vesicles as drug carriers may have much less adverse effects in patients compared to synthetic drug carrier molecules.

Almost all naturally occurring phospholipids are constructed from the combination of a polar headgroup and a glycerol backbone moiety substituted with either one or two acyl or alkyl chains or an *N*-acylated sphingoid base (i.e., a ceramide). Therefore, the phospholipids from natural sources can be classified into phosphodiglycerides and sphingolipids, together with their corresponding hydrolysis products. The basic structures of these two classes are illustrated in Figure 14.2.

Phosphatidylcholines (PC) are the major phosphodiglycerides that can be obtained from natural and synthetic sources. When extracted from plant and animal sources (primarily egg yolk and soybean), PCs, known in the unpurified form as *lecithins*, are composed of a mixture of PCs varying in chain length and degree of unsaturation. Unless highly purified, these naturally derived