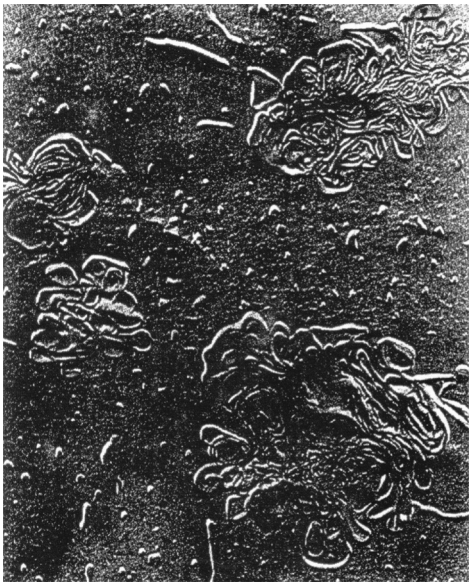

FIGURE 14.9 Freeze-fracture electron micrograph of the ribbon-like amphotericin B lipid complexes. (From Bangham, A. D., *Hosp. Pract.*, 27, 51–62, 1992. With permission.)

Amphotericin B lipid complex (Abelcet®, Enzon Pharmaceuticals, Inc., Bridgewater, New Jersey) is a suspension of ribbonlike structures of a bilayered membrane formed by combining a 7:3 molar ratio of DMPC and DMPG with amphotericin B (Figure 14.9). Amphotericin B colloidal dispersion (Amphotec®, developed by Sequus and now marketed by Three Rivers Pharmaceuticals) is composed of disk-like structures of cholesteryl sulfate complex with amphotericin B in a ratio of 1:1. Ambisome® (developed by Gilead Sciences and now marketed by Astellas Pharma US, Deerfield, Illinois) is the only true liposomal preparation among the three lipid formulations of amphotericin B. In this formulation, the drug is incorporated into the bilayer of small unilamellar liposome within a size range of 45–80 nm. The lipid bilayer is made up of hydrogenated soy phosphatidylcholine (HSPC), distearoyl phosphatidylglycerol (DSPG), cholesterol, and amphotericin B in a 2:0.8:1:0.4 molar ratios (Adler-Moore and Proffitt, 1993). In the development of this formulation, unilamellar liposomes with a range of different chemical compositions were tested. Although both HSPC and hydrogenated egg phosphatidylcholine performed comparably as the primary phospholipid, HSPC was chosen for the final formulation since there was less variation in the length of its hydrocarbon chains. Hydrogenated rather than nonhydrogenated phospholipids were used because of the chemical stability provided by the saturated phospholipids. Formulations that contained no cholesterol or low molar ratios of cholesterol exhibited more toxicity in mice than formulations with a cholesterol content greater than 25 mol% of total lipid component. The reduced toxicity associated with the presence of cholesterol in AmBisome may be due to increased bilayer stability that is imparted by the sterol, and possibly to the affinity of Amphotericin B for the cholesterol in the membrane (Papahadjopoulos et al., 1973a, b; Medoff et al., 1983). Increased toxicity was also observed in mice either when the molar ratio of DSPG: amphotericin B was less than 2:1 or when shorter chain phospholipids, such as dilauryl phosphatidylglycerol, were substituted for DSPG (Adler-Moore and Proffitt, 1993).

In the manufacturing process for the marketed products, the lipids, cholesterol, and amphotericin B were first dissolved in an organic solvent, and a dry film was obtained using a rotary evaporator. The film was dehydrated and a microemulsification technique (Gamble, 1988) was used in the preparation of small unilamellar liposomes. In the microemulsification process, a modified Gaulin