active pharmaceutical ingredient subsequently is slowly released as the polymer degrades. For Atrigel® formulations, a biodegradable polymer is dissolved in a biocompatible carrier. Biodegradable polymers include primarily poly(DL-lactide), lactide/glycolide copolymers, or lactide/caprolactone copolymers. Solvents used to dissolve these polymers include *N*-methyl-2-pyrrolidone (primary), polyethylene glycol (PEG), tetraglycol, glycofurol, triacetin, ethyl acetate, and benzyl benzoate. Indeed, any organic solvent used must be safe, biocompatible, water miscible, and easily used in a manufacturing environment.

Dextran-based microspheres encapsulate liposomes and proteins using an aqueous-based emulsion technique tailored for solvent-unsuitable drugs. ProMaxx® (Baxter-Epic) is based on completely aqueous systems to form well-controlled, uniform microspheres allowing high drug loading. Microspheres, containing the active and excipients such as dextran sulfate, hydroxyethyl starch, and albumin, are formed through patented adjustments of ionic strength, pH, active and polymer concentrations, and temperature. Promaxx® microsphere technology is unique because microspheres are manufactured without the need for organic solvents.

Other microsphere formulations meeting clinical or commercial success include Chroniject™, ProLease®, Medisorb®, and SABER™.

Some additional coverage of microspheres is found in chapter 9.

Liposomes

In recent years more liposomal formulations have been commercially available. Table 3-3 shows examples of marketed liposome products where the application of liposome technology has moved beyond formulations containing either doxorubicine or amphotericin. In 1995, Sequus marketed the first stealth liposome (Doxil). Stealth liposomes are nanoparticles with special polyethylene derivatives that allow the liposome to avoid detection by the reticuloendothelial system that normally would update these injected particles and minimize their circulation to the appropriate receptor sites. Earlier problems with economic and reproducible large-scale production of liposomes have been largely solved.

Liposomal-based technologies have been used to deliver genetically engineered, nonviral plasmids across cellular barriers that target brain cancer. This is also called RNAi (RNA interference) technology that inhibits a growth factor responsible for keeping cancer cells alive.

Other examples of liposome technology—Pacira's multivesicular liposome formulation (DepoFoam™), Neopharm's NeoLipid™, and Genzyme's Lipobridge™. DepoFoam™

Table 3-3 Examples of Commercial Injectable Liposome Products

Drug product	Drug substance	Delivery matrix[a]	Other excipients	Delivery technology
Abelcet® (Enzon)	Amphotericin B	DMPC, DMPG	Sodium chloride	Lipid complex
AmBisome® (Astellas)	Amphotericin B	HSPC, cholesterol, DSPG	Vitamin E, disodium succinate hexahydrate	Liposome
Amphotec®	Amphotericin B	Cholesterol sulfate	Tromethane, disodium EDTA, lactose (lyophilized powder)	Colloidal dispersion
DepoCyte® (Pacira/Enzon)	Cytarabine	DOPC, DPPG, cholesterol, triolein	Triolein	Liposome
DepoDur (Pacira/EKR)	Morphine	DOPC, DPPG, cholesterol	Tricaprylin, triolein	Liposome
Doxil® (Ortho Biotech)	Doxorubicin	MPEG-DSPE, HSPC, cholesterol	Ammonium sulfate, histidine	Stealth liposomes
Visudyne® (Novartis)	Verteporfin	Ascorbyl palmitate, BHT, DMPC	Lactose	Liposome

[a]DMPC, 1,2-dimyristoyl-sn-glycero-3-phosphocholine, DMPG, 1,2-myristoyl-sn-glycero-3[phospho-rac-(1-glycerol . . .)]; HSPC, fully hydrogenated soy phosphatidylcholine; DSPG, 1,2-distearoyl-sn-glycero-3[phospho-rac-(1-glycerol . . .)]; DOPC, 1,2-dioleoyl-sn-glycero-3-phosphocholine; DPPG, 1,2-dipalmitoyl-sn-glycero-3[phospho-rac-(1-glycerol . . .)]; MPEG-DSPE, *N*-(carbonyl-methoxy PEG 2000)-1,2-distearoyl-sn-glycero-3-phosphoethanolamine: liposome coating that keeps immune system from recognizing liposome as a foreign body.