effect on the pharmacokinetic properties of doxorubicin, which contributes to its increased therapeutic index. The half-lives are 30, 16, and 74 hours, while the volumes of distribution are 900 L/m^2, 34 L/m^2, and 1.9 L/m^2 for free doxorubicin, non-pegylated liposomal doxorubicin, and pegylated liposomal doxorubicin, respectively, (Macpherson and Evans, 2009).

Doxil is manufactured by the remote loading technique discussed earlier, which allows high loading of the drug in the liposomes. The drug actually precipitates inside the liposome, which increases loading and retention within the liposome (Allen and Cullis, 2013). Doxil has become one of the most widely used agents for treatment of ovarian cancer, AIDS-related Kaposi's sarcoma, multiple myeloma, and breast cancer. Due to manufacturing issues, there was a drug supply shortage in 2011; the FDA allowed temporary use of an alternate form (Berger et al., 2014), and eventually an alternate manufacturing site for Doxil was approved to alleviate the shortage.

Paclitaxel

Paclitaxel, a natural diterpene product isolated from the bark of *Taxus brevifolia*, is clinically active against advanced ovarian and breast cancer. Its use in treating other malignancies such as head, lung, and neck cancers is being explored. Paclitaxel is the first of a new class of antineoplastic drugs (Rowinsky et al., 1990; Huizing et al., 1995). The unique mechanism of action of paclitaxel includes stabilization of abnormal microtubules (Schiff et al., 1979), thus interfering with tumor cellular progress through mitosis, and arresting cell replication (DeBrabander et al., 1981). In spite of its powerful antitumor activity, the drug has presented a considerable challenge to formulation scientists owing to its poor water solubility. It does not contain any functional ionizable groups (Wani et al., 1971). For this reason, the solubility problem cannot be improved by alteration of pH, salt formation, or addition of charged complexing agents. The current clinical dosage form, Taxol® consists of concentrations of 0.3–1.2 mg/mL of paclitaxel dispersed in an equal parts mixture of ethanol and polyethoxylated castor oil (Cremophor EL®) (Meerum et al., 1997). This formulation is associated with a number of concerns, including stability, filtering requirements, and use of nonplasticized solution containers, and administration sets. Moreover, some of the side effects, such as severe hypersensitivity reactions, are considered to be formulation related. The adverse effects of the formulation are considered to be related to the use of Cremophor EL as the vehicle (Lorenz et al., 1977; Liebmann et al., 1994).

To eliminate the side effects caused by the excipients and possibly increase the antitumor activity of paclitaxel, liposome formulations have been investigated (Sharma et al., 1993; Straubinger et al., 1993; Sharma and Straubinger, 1994). The rationale of using liposomes as a carrier for the water-insoluble paclitaxel is similar to that for amphotericin B. More than 300 liposome formulations were evaluated. Preliminary results suggested that using PC as the principal lipid can incorporate higher concentrations of paclitaxel than any other lipids. However, the formulation containing only PC was highly aggregated, and incorporation of a negatively charged lipid, PG, reduced the aggregation. A molar ratio of PC:PG 9:1 was selected based on the stability results, as indicated by the crystallization of paclitaxel from the aqueous liposomal formulations (Sharma and Straubinger, 1994).

The production process of paclitaxel liposome formulation was similar to that of amphotericin B. However, owing to the very low solubility of paclitaxel, several different procedures were involved. First, solvation of the lipid-drug film was done using tert-butanol. Second, the solution was then lyophilized for 24 h. The lyophilized powder was hydrated with buffer (NaCl/Tes/EDTA:14 mM/10 mM/0.1 mM). Third, in the size-reduction process, a sonication method was used, wherein the suspension of MLVs was sonicated under argon in a bath sonicator for 30 min at 20°C. On the basis of the method, SUVs can be obtained with the size range of 25–50 nm. Paclitaxel was stable in the liposome for more than 3 months at both 4°C and 20°C, as indicated by a reverse-phase HPLC method. The liposomal formulations have been demonstrated to be able to increase the therapeutic index of paclitaxel in human ovarian tumor models (Sharma et al., 1997). A commercial liposomal formulation of paclitaxel, EndoTAG® (MediGene), is currently in Phase III clinical trials, while another, LEP-ETU (Neopharm/Insys) is in Phase II trials (Table 14.2).