used in an o/w emulsion has a required HLB value (e.g., 6–7 for cottonseed oil and 14 for castor oil). An emulsion is most stable when a surfactant or combination of surfactants has a HLB value close to that required HLB value of the oil phase.

Other Components

As is being discussed, antioxidants may need to be included in a parenteral emulsion product if unsaturated lipids are present. Agents such as glycerol are also typically added to adjust tonicity. As bacteria can grow in the aqueous phases of emulsions, an adequate concentration of an antimicrobial preservative agent should be added. To achieve antimicrobial effect, the levels of antimicrobial agents with relatively high affinity to the oil phase of an emulsion (e.g., benzyl alcohol and parabens) will be higher than those that would be needed in single-phase liquid formulations. The antimicrobial agents should also be nonionized and not bound to other components of the emulsion to penetrate the bacterial membrane. Some hydrophilic antimicrobial agents (e.g., benzoic acid and ascorbic acid) are effective only at acidic pH, owing to formation of ionic forms at basic pH. The effects of these antimicrobial agents on the stability of the emulsion should also be considered during formulation development.

MARKETED EMULSION PRODUCTS

Topical medications have been formulated as o/w or w/o emulsions (e.g., lotions and ointments) for centuries and marketed by pharmaceutical companies for many decades. These applications are beyond the scope of this chapter, since the purpose of using an emulsion in topical formulations is generally to aid in spreading and penetration properties rather than for drug solubilization. Emulsions have also been used for some time as IV nutritional mixtures (total parenteral nutrition) to supply high-caloric lipids. These are generally emulsions of soybean, sesame, or safflower oil (10%–20%) emulsified with phospholipids, for example, egg lecithin containing 60%–70% PC. Liposyn® and Intralipid®, manufactured by Hospira and Kabi Vitrum, respectively, are two examples of the most widely used total parenteral emulsions; they contain 10%–20% soybean oil (Intralipid) or safflower oil (Liposyn), 1.2% egg phosphatides as emulsifier, and 2.5% glycerol. Another example is Lipofundin® (Braun), which contains 10%–20% soybean or cottonseed oil, 0.75% soybean phosphatides, 5% xylitol or sorbitol, and 0%–0.6% α-tocopherol. Other examples are Trive 1000® (Egic), Nutrafundin® (Braun), as well as Intralipid-type products marketed by Travenol, Green Cross, and Daigo (Hansrani et al., 1983). Parenteral nutrition emulsions such as Liposyn and Intralipid have recently been used in clinical therapy to treat drug and toxicity in cases of overdosage of a variety of lipid-soluble drugs such as anesthetics, antipsychotics, antidepressants, anti-arrhythmics, and calcium channel blockers (Cave et al., 2014; Muller et al. 2015); the proposed mechanism of action is sequestration of the drugs into an intravascular *lipid sink* of the emulsion to reduce to free drug concentration (Waring, 2012; Clark et al. 2014).

Development of drug-containing emulsions for parenteral use have been much less common. Drug-emulsion formulations marketed in Japan, Europe, and the United States for IV use are given in Table 10.3. The drug in these formulations (diazepam; propofol; prostaglandin E1; etomidate; vitamins A, D, E, and K; dexamethazone palmitate; flubiprofen; perflurodecalin; docetaxel; and cyclosporine) are all poorly water soluble, rationalizing use of an emulsion system for solubilization and improved delivery. In the blood substitute Fluosol-DA product, the *drug* is actually the oil phase of the emulsion that solubilizes oxygen. In 2008, an emulsion formulation of clevidipine (Cleviprex®), was approved for treatment of hypertension. Clevidipine is a calcium channel blocker that is practically insoluble in water; it is solubilized in a soybean oil/egg phospholipid/oleic acid emulsion for injection (Erickson et al. 2010). Ciclomulsion® is an cyclosporine emulsion formulation in which the drug is solubilized in a soybean oil/MCT/egg lecithin/sodium oleate emulsion. In development by NeuroVive Pharmaceutical, it is in Phase III clinical trials for the treatment of