

# Water-Insoluble Drug Formulation

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# 10 Emulsions, Microemulsions, and Lipid-Based Drug Delivery Systems for Drug Solubilization and Delivery—Part I: Parenteral Applications

*John B. Cannon, Yi Shi, and Pramod Gupta*

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## INTRODUCTION

Over the past several decades, emulsion formulations have been explored for resolving a variety of drug delivery challenges. Unlike solutions for oral or parenteral administrations, which are usually homogeneous one-phase systems or molecular dispersions, emulsions are colloidal dispersions of at least two immiscible phases stabilized with the aid of a third component generally referred to as the emulsifying agent. Most of the advantages of emulsion systems over conventional dosage forms such as oral solutions and liquid injectables can be attributed to this stable heterogeneity, and their ability to deliver immiscible phases in a reliable and reproducible manner. This chapter focuses on demonstrating the usefulness of emulsion systems for the delivery of water-insoluble compounds for parenteral administration. Following some basic definitions and general properties of emulsions, their potential utility for parenteral delivery of lipophilic compounds is rationalized. Wherever possible, examples of experimental and clinical use of emulsion formulations for parenteral delivery of water-insoluble compounds are provided. The challenges encountered in development of these formulations are also discussed. Finally, the utility of this approach is compared with other pharmaceutical techniques of drug solubilization.

## EMULSIONS AS PHARMACEUTICAL DOSAGE FORMS

### DEFINITIONS

An emulsion can be defined as a mixture of two immiscible phases (namely, water and oil) with an emulsifier added to stabilize the dispersed droplets (Davis et al., 1987). As conventionally defined, emulsions will have droplet diameters of more than 100 nm (up to 50  $\mu\text{m}$ ), and thus are opaque or milky in appearance. In addition, they are thermodynamically unstable by nature, that is, on standing they will eventually separate into two phases. However, proper choice of emulsifier (generally 1–5%) and preparation conditions can delay this separation and thus lead to nominal shelf lives of more than 2 years, as typically required for pharmaceutical products. An emulsion can be characterized as oil-in-water (o/w) (containing up to 40% oil) or water-in-oil (w/o), depending on the identity of the dispersed and continuous phases. Multiple (e.g., w/o/w) emulsions can also be prepared, but these are less widely used in pharmaceutical applications.

In contrast to the conventional emulsions or macroemulsions described earlier are the disperse systems currently termed *microemulsions*. The term was first introduced by Schulman in 1959 to describe a visually transparent or translucent thermodynamically stable system, with much smaller droplet diameter (6–80 nm) than conventional emulsions. In addition to the aqueous phase, oily phase, and surfactant, they have a high proportion of a “cosurfactant,” such as an alkanol of 4–8 carbons or a nonionic surfactant. Whereas microemulsions have found applications in oral use (as described in the next chapter), parenteral use of microemulsions has been less common owing to toxicity concerns (e.g., hemolysis) arising from the high surfactant and cosolvent levels. In one example, microemulsions composed of PEG/ethanol/water/medium-chain triglycerides/Solutol HS15/soy phosphatidylcholine have been safely infused into rats at up to 0.5 mL/kg. On dilution into water, the microemulsion forms a o/w emulsion of 60–190 nm droplet size (Von Corswant et al., 1998).

Typically, emulsions for parenteral use should have droplet size less than 1  $\mu\text{m}$  (generally 100–1000 nm), and hence are often called “submicron emulsions,” or (less properly) “nanoemulsions.” Use of the latter term is unfortunate and can lead to confusion, since their droplet size is actually larger than the microemulsion systems described earlier. The term “nanoemulsion” has been proposed to include metastable emulsions  $\leq 100$  nm as well as thermodynamically stable microemulsions (Sarker, 2005). Manufacture of submicron emulsions require special homogenization equipment, as will be described later.

**TABLE 10.1****Lipids Approved for Clinical Use in Parenteral Lipid-Based Formulations**

| Class                       | Trade or<br>Common Name         | Chemical Name                                    |
|-----------------------------|---------------------------------|--------------------------------------------------|
| LCTs                        | Triolein                        | (Z)-9-Octadecenoic acid 1,2,3-propanetriyl ester |
|                             | Soybean oil                     |                                                  |
|                             | Safflower oil                   |                                                  |
|                             | Sesame oil                      |                                                  |
|                             | Cottonseed oil                  |                                                  |
|                             | Castor oil                      |                                                  |
| MCTs                        | Fractionated coconut oil        | MCTs                                             |
|                             | Miglyol <sup>®</sup> , 810, 812 |                                                  |
|                             | Neobee <sup>®</sup> M5          |                                                  |
|                             | Captex <sup>®</sup> 300         |                                                  |
| Fatty acids and derivatives | Oleic acid                      | (Z)-9-Octadecenoic acid                          |
|                             | Ethyl oleate                    | (Z)-9-Octadecenoic acid, ethyl ester             |
| Novel lipids                | Vitamin E                       | D- $\alpha$ -Tocopherol                          |

**COMPONENTS OF EMULSIONS USED FOR PARENTERAL APPLICATIONS**

A typical parenteral o/w emulsion is composed of lipid droplets (10–20%), emulsifier, and osmotic agent; it is administered by either intravenous (IV) bolus or IV infusion. In addition, when an emulsion formulation is packed in a multidose container, antimicrobial agents should be included in the formulation to prevent the growth of microorganisms.

**Lipids**

The operational definition of lipids are those components of biological material that are water insoluble but soluble in organic solvents such as methylene chloride; lipids can encompass not only naturally occurring lipophilic materials but also those easily derived from lipids that occur naturally. Table 10.1 summarizes the lipids most commonly used in parenteral emulsions. Long- (LCT) and medium-chain triglycerides (MCT), either alone or in combination, are used in commercial parenteral emulsions owing to their long history of safety. LCT are derived from vegetable sources such as soybean oil, safflower oil, sesame oil, and cottonseed oil, whereas, MCT are obtained by re-esterification of fractionated coconut oil (mainly caprylic and capric fatty acid). Other lipids have also been investigated for use in parenteral emulsions. Ethyl oleate can be used as the oil phase in emulsions for intramuscular or subcutaneous administration. Oleic acid has been used experimentally for parenteral emulsions; it is used in a number of commercial oral products. D- $\alpha$ -Tocopherol (vitamin E) has been recently investigated as a novel lipid for parenteral emulsions (Constantinides et al., 2004). A study has shown that D- $\alpha$ -tocopherol was well tolerated in patients receiving a daily IV administration of D- $\alpha$ -tocopherol at doses up to 2300 mg/m<sup>2</sup> for 9 consecutive days (Helson, 1984), but the safety of higher doses or chronic use of D- $\alpha$ -tocopherol needs to be further evaluated. Recently, marine oils containing large quantities of long-chain omega-3 polyunsaturated fatty acids have drawn lots of attention because of their health benefits. Parenteral emulsions prepared from marine oils have also been reported (Ton et al., 2005; Cui et al., 2006).

**Surfactants**

Surfactants are commonly used to stabilize the emulsion by reducing interfacial tension between the oil and the water phases. Although a variety of surfactants are available, only a few are used in

**TABLE 10.2**  
**Surfactants Used in Parenteral Emulsions**

| Chemical or<br>Common Name                          | Trade Name                    | HLB                | Recommended<br>Concentration (%) |
|-----------------------------------------------------|-------------------------------|--------------------|----------------------------------|
| Polyoxyl 35 castor oil                              | Cremophor® EL                 | 12–14 <sup>a</sup> | 10                               |
| Polyoxyethylene-660-hydroxystearate                 | Solutol® H15                  |                    |                                  |
| Polyoxyethylene sorbitan monolaurate                | Polysorbate 20 (Tween® 20)    | 16.7 <sup>a</sup>  |                                  |
| Polyoxyethylene sorbitan monolaurate                | Polysorbate 40 (Tween® 40)    | 15.6 <sup>a</sup>  |                                  |
| Polyoxyethylene sorbitan monolaurate                | Polysorbate 80 (Tween® 80)    | 15.0 <sup>a</sup>  |                                  |
| Sorbitan monolaurate                                | Span® 20                      | 8.6 <sup>a</sup>   | 0.01–0.05 <sup>a</sup>           |
| Sorbitan monopalmitate                              | Span® 40                      | 6.7 <sup>a</sup>   | 0.01–0.05 <sup>a</sup>           |
| Sorbitan monooleate                                 | Span® 80                      | 4.3 <sup>a</sup>   |                                  |
| Sorbitan trioleate                                  | Span® 85                      | 1.8 <sup>a</sup>   | 0.01–0.05 <sup>a</sup>           |
| Polyoxyethylene-polyoxypropylene<br>block copolymer | Poloxamer 188 (Pluronic® F68) | 29 <sup>b</sup>    | 0.3 <sup>a</sup>                 |
| 7-Desoxycholic acid sodium                          | Bile salt                     | 26                 |                                  |
| Phosphatidylcholine                                 | Phospholipon® 90              |                    | 1–3                              |

<sup>a</sup> Reference from *Handbook of Pharmaceutical Excipients*, 1994.

<sup>b</sup> Reference from Vendor information.

approved parenteral emulsion products. The most commonly used surfactant in parenteral products is lecithin [phosphatidylcholine (PC)], which is a natural emulsifying agent derived from egg yolk or soybean. Sodium deoxycholate (bile salt) is also a natural surfactant that has been used in marketed parenteral products (e.g., Fungizone®). Other surfactants that have been used in parenteral products are synthetic nonionic surfactants including Cremophor® EL (Polyoxyl-35 castor oil), Solutol® HS-15 (polyoxyethylene-660-hydroxystearate), Tween® 20, 40, and 80, Span® 20, and Poloxamer 188. Poloxamer 188 has been shown to be superior in stabilizing emulsion during autoclaving comparing to other surfactants (Jumaa and Muller, 1998). However, large volume or long-term administration of Poloxamer 188 need to be evaluated. The allowed concentration for administration for each of the surfactants is listed in Table 10.2.

### HLB Classification System and Required HLB

The hydrophilic–lipophilic balance (HLB) classification system was first introduced by Griffin (1949) to characterize the relative affinity of a surfactant to the aqueous and oil phase. A HLB value is an empirical numerical value in the range of 1–30. The higher the HLB value, the more hydrophilic the surfactant is; and in turn, the lower the HLB value, the more lipophilic the surfactant is. As a result, surfactants with higher HLB values (>8) are favorable for formation of o/w emulsions, while surfactants with lower HLB values (3–6) are more suitable for the formation of w/o emulsions. The HLB values of the surfactants used in parenteral emulsions are listed in Table 10.2.

The HLB value of surfactants that provides the lowest interfacial tension between the oil and water phases for a given lipid mixture is called the required HLB. Each of the lipophilic ingredients 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 have 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%  $\alpha$ -tocopherol. Other examples are Trive 1000® (Egic), Nutrafundin® (Braun), as well as Intralipid®-type products marketed by Travenol, Green Cross, and Daigo (Mansrani et al., 1983). 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; 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. The brevity of the list illustrates the historical reluctance of the pharmaceutical industry to use emulsions as a formulation tool in the parenteral drug delivery areas, perhaps owing to parenteral safety concerns, difficulty in manufacturing, perceived lack of patient acceptability, or other concerns. This should hopefully change on the basis of recent experience with emulsions, some of which are outlined in this chapter.

## PREPARATION OF EMULSIONS

Preparation of an emulsion requires mixing the two immiscible phases with the surfactant(s) and applying energy (generally mechanical) to create shear forces to deform the interface and form droplets, using sufficient force and time to achieve the required droplet size. There are a variety of devices that will accomplish this in either batch or continuous modes of operation. The forces involved in the emulsification process are not completely understood, but the methods can be classified according to three mechanisms. Laminar flow can be envisioned as the moving together of layers of the two phases, with resultant viscous forces leading to droplet formation and size reduction. Pipe flow devices, colloid mills, and ball and roller mills are based on laminar flow mechanisms. Turbulence, on the other hand, forms eddies or swirls, and the resulting inertial forces contribute to the emulsification process; shaking or injection can achieve the required turbulence. Cavitation involves the transient formation of small vapor bubbles that collapse extremely fast, and the resulting shock waves cause droplet formation and disruption; ultrasonic devices emulsify by this mechanism, along

**TABLE 10.3**  
**A Representative List of Marketed Emulsion Products Containing Water-Insoluble Drugs**

| Drug                                          | Product Name                   | Company                          | Route                 | Drug Activity               | Product Status                                        | References                                                                                                    |
|-----------------------------------------------|--------------------------------|----------------------------------|-----------------------|-----------------------------|-------------------------------------------------------|---------------------------------------------------------------------------------------------------------------|
| Diazepam                                      | Diazemuls®<br>Diazepam®-Lipuro | Braun Melsungen                  | IV                    | Sedation                    | Marketed in Europe,<br>Canada, and Australia          | Collins-Gold et al. (1990)                                                                                    |
| Etomidate                                     | Stesolid                       | Dumex (Denmark)                  | IV                    | Sedation                    | Marketed in Europe                                    | Collins-Gold et al. (1990)                                                                                    |
| Prostaglandin E1                              | Etomidat®-Lipuro<br>Lipile     | Braun Melsungen<br>Green Cross   | IV<br>IV              | Anesthesia<br>Vasodilator   | Marketed in Europe<br>Marketed in Japan               | Collins-Gold et al. (1990);<br>Yamaguchi et al. (1994)<br><i>Physicians Desk Reference</i> ,<br>p. 828 (2004) |
| Propofol                                      | Propofol<br>Diprivan®          | Baxter Anesthesia<br>AstraZeneca | IV<br>IV              | Anesthesia<br>Anesthesia    | Marketed in United States<br>Marketed worldwide       | Collins-Gold et al. (1990);<br><i>Physicians Desk Reference</i> ,<br>p. 663 (2004)                            |
| Vitamins A, D, E and K                        | Propofol®-Lipuro               | Braun                            | IV                    | Anesthesia                  | Marketed in Europe                                    | Kam et al. (2004)                                                                                             |
| Dexamethazone                                 | Vitalipid®                     | Kabi                             | IV                    | Nutrition                   | Marketed in Europe                                    | Collins-Gold et al. (1990)                                                                                    |
| palmitate                                     | Limethason<br>(Lipotalon)      | Green Cross<br>Merckle           | Intra-arthritis<br>IV | Corticosteroid<br>Analgesia | Marketed in Japan and<br>Germany<br>Marketed in Japan | Yamaguchi et al. (1994)<br><i>Physicians Desk Reference</i> ,<br>p. 593 (1995)                                |
| Flurbiprofen                                  | Lipfen®                        | Green Cross                      | IV                    | Blood substitute            | Marketed worldwide                                    | Yamaguchi et al. (1994);<br><i>Physicians Desk Reference</i> ,<br>p. 556 (2004)                               |
| Perfluorodecalin +<br>perfluorotripropylamine | Fluosol-DA                     | Green Cross; Alpha               | Intracoronary         |                             |                                                       |                                                                                                               |
| Cyclosporine A                                | Restasis™                      | Allergan                         | Ophthalmic            | Immunomodulator             | Marketed in United States                             |                                                                                                               |

with turbulence. Rotor–stator and similar stirring devices emulsify by combination of turbulence and laminar flow mechanisms, while high-pressure homogenizers emulsify by combination of all three mechanisms. While most of the methods can be adapted for laboratory use, only rotor–stator stirrers, colloid mills, high-pressure homogenizers, and ultrasonic devices are practical for large-scale production (Walstra, 1983).

Since nutritional emulsions (e.g., Liposyn® and Intralipid®) have been in widespread use for several decades, procedures for large-scale manufacture of pharmaceutically acceptable o/w emulsions are now fairly well developed. Typically, the surfactant is dispersed in the aqueous phase along with any water-soluble components (e.g., glycerol for adjustment of tonicity) by stirring and heating as necessary until a homogenous mixture is formed. The oil phase is then added with stirring or shaking to form a “premix” with large ( $>10\ \mu\text{m}$ ) droplets, which is then subjected to a high-energy mechanical homogenization using one of the methods described earlier. The final droplet size depends on the formulation composition as well as the operating conditions (e.g., temperature, homogenization pressure, and duration of homogenization) (Collins-Gold et al., 1990).

Several apparatus are available for the manufacture of pharmaceutical emulsions: the Gaulin® and Rannie® homogenizers are the most commonly used devices for large-scale manufacture; the Microfluidizer® and Five Star® Technologies Homogenizer are adaptable for laboratory or pilot scale preparations. Whatever device is used, procedures must be developed for validation of GMP-related issues such as drug losses owing to shear forces, product sterility, equipment cleaning, and product contamination from earlier uses.

When an emulsion is used for drug delivery, depending on the drug properties, one can envision several avenues by which the drug can be introduced into the emulsion. The simplest case would be if the drug is sufficiently lipophilic so that it can be readily dissolved in the oil phase before premix formation. Examples of *de novo* preparations shown in Table 10.3 are an emulsion containing Prostaglandin E1 (PGE1) and Vitalipid®, an emulsion containing oil-soluble vitamins. Similarly, penclomedine is soluble up to 100 mg/mL in soybean oil, allowing preparation of an emulsion with 10% soybean oil and 4.7 mg/mL final drug concentration (Prankerd and Stella, 1990). In some cases, an oil-soluble drug can be added directly to an already-prepared emulsion (e.g., Liposyn® or Intralipid®) and the drug preferentially partitions into the oil phase. In general, drugs that are liquid at room temperature are most amenable for these extemporaneously prepared emulsions, since the dissolution and required partitioning may be too slow for a solid drug. Anesthetics often meet this criteria. Examples are halothane and propofol: the latter is marketed as Diprivan®, an Intralipid®/Liposyn® type emulsion containing 1% propofol and 10% soybean oil.

If a drug has sufficient water solubility, one can dissolve it into the aqueous component of the emulsion before formation of the premix for *de novo* emulsion preparation, or add the drug to a preformed emulsion for extemporaneous preparation. In these cases, knowledge of the oil–water partition coefficient is important to predict the final distribution of drug within the oil phases. If the drug is ionizable, one may be able to incorporate the drug by pH adjustment, that is, add the drug to the aqueous phase at a pH at which it is ionized and thus more water soluble, and then adjust the pH to a region in which it is nonionized and thus more hydrophobic, favoring partitioning into the oil phase.

Unfortunately, there are many drugs that have little or no solubility in either water or oil. In such a case, the final locale of drug would usually be the interface of the emulsion droplet, and emulsion preparation may be problematic. Nevertheless, several strategies have been devised for successful preparation of emulsions containing drugs in this category. Probably the most commonly used approach is the use of a cosolvent in which the drug is highly soluble; the drug solution can then be added extemporaneously to an emulsion, or to the oil phase before premix formation in a *de novo* preparation. Suitable pharmaceutically acceptable cosolvents include ethanol, propylene glycol, PEG300, dimethylacetamide, triacetin, and mixtures of these solvents. However, the effect of cosolvent on chemical stability, emulsion droplet size, and drug partitioning must be carefully assessed. Diazemuls® is a diazepam (Valium) emulsion marketed in Denmark; it

contains 5% acetylated monoglycerides as the cosolvent along with 15% soybean oil, 1.2% egg phospholipids, and 2.25% glycerol (Collins-Gold et al., 1990). Amphotericin B emulsions have been prepared by a similar technique, wherein the drug is dissolved in dimethylacetamide to introduce the drug into the emulsion (Kirsch and Ravin, 1987). Similarly, triacetin allows preparation of a paclitaxel emulsion (Tarr et al., 1987), and addition of a solution of the chemotherapeutic agent Perilla ketone in 10% ethanol/40% propylene glycol/50% water to Intralipid® results in a 1 mg/mL drug formulation (Collins-Gold et al., 1990). The same solvent mixture has been used to prepare an emulsion of Rhizoxin in 10% Intralipid® (Pranker and Stella, 1990). If the cosolvent is volatile, one can effect its removal following emulsion preparation. Such was the case for an amphotericin B emulsion, wherein methanol was used to introduce the drug and then allowed to evaporate from the formulation before emulsification with the oil (Forster et al., 1988). A similar approach involves the use of lipophilic counterions to increase the solubility of the drug in oil, allowing extemporaneous or de novo preparation of the emulsion. In this manner clarithromycin was dissolved in a fatty acid/oil mixture (e.g., oleic acid/soybean oil or decanoic acid/Neobee® MCT oil) that was then formulated to obtain an o/w emulsion (Lovell et al., 1994). Another approach would be to solubilize the drug with an appropriate detergent and add this to an emulsion. For example, amphotericin B emulsions for clinical use have been prepared by dispersing lyophilized Fungizone® into Intralipid® 20% rather than into dextrose as is the standard practice; the presence of the deoxycholate in Fungizone® apparently allows solubilization of the drug and partitioning into the emulsion droplet (Caillot et al., 1992). However, the validity of this approach has been questioned, since undissolved amphotericin B has been detected in such preparations (Davis, 1995).

If phospholipid dispersions (liposomes) of the drug can be prepared, one can envision addition of the oil phase to the drug liposomes, followed by emulsification, to give a drug emulsion, as was done to prepare an amphotericin B emulsion (Davis et al., 1987; Forster et al., 1988). If the drug is present in the lipid bilayer of the original liposomes, it will probably remain at the interface of the resulting emulsion. A simpler approach was used to prepare an emulsion of Almitrine, whereby a drug-phospholipid solution in chloroform/methanol solution was rotary evaporated to form a drug-lipid film (the first step in the classical method for liposome preparation), which was then hydrated with 10% Intralipid® to form an emulsion. However, it was reported that drug crystals formed within several weeks of the preparation of this emulsion (Van Bloois et al., 1987).

Recently a solvent-free approach (SolEmuls®) using high-pressure homogenization to incorporate poorly soluble drugs in parenteral emulsions has been reported by Muller et al. (2004). Powdered drug or finely milled drug suspension is added to a commercial emulsion (e.g., Lipofundin® or Intralipid®) by stirring. Alternatively, the drug can be admixed during the de novo production of emulsion. The obtained dispersion containing oil droplets and drug particles is then subjected to high-pressure homogenization. The high streaming velocities lead to drug dissolution and partitioning into the interfacial layer. Stable emulsion formulations of several poorly soluble drugs including ketoconazole, itraconazole, carbamazepine, and amphotericin B have been prepared using these methods. A 1 mg/mL itraconazole emulsion with mean particle size of 255 nm has been shown to be stable at room temperature for 9 months and no drug crystal was observed under microscopic examination (Akkar et al., 2004). As the interfacial layer could only solubilize a certain amount of drug, exceeding the saturation concentration of the drug at the interfacial layer, hybrid dispersions consisting of drug-loaded oil droplets and drug nanocrystals could form. Tiny crystals were found in a 2 mg/mL amphotericin B emulsion using polarized microscope (Müller, 2004).

In the case of parenteral emulsions, insuring the sterility of the product is crucial. The preferred method for sterilization is generally terminal autoclaving. The nutritional emulsions such as Intralipid® and Liposyn® can be sterilized by autoclaving without phase separation or other stability problems (Washington et al., 1993). However, autoclaving has been found to cause some hydrolysis of lipids and lecithins resulting in liberation of free fatty acids, which lowers the pH of the emulsions. To counter the pH dropping during autoclave, it is suggested to adjust the pH of the emulsion to slightly alkaline pH (8.0) before autoclaving (Floyd, 1999). If the components of a particular

drug-emulsion formulation preclude autoclaving owing to stability problems, sterile filtration of the product may be a viable alternative, requiring that the emulsion droplets pass through a 0.22  $\mu\text{m}$  pore (Lidgate et al., 1992). There are also some reports of emulsions being successfully lyophilized; for example, an HIV protease inhibitor, AG1284, was solubilized in an Imwitor<sup>®</sup> 742/Tween 80/Span 80 emulsion, which could be lyophilized and reconstituted without loss of viability and potency (Chiang et al., 1995).

## CHARACTERISTICS OF EMULSIONS

There are a number of physical-chemical properties of emulsions that are important to consider when developing an emulsion formulation for a drug. These include, but are not limited to, particle (droplet) size, viscosity, osmolarity, and zeta potential, which are used to monitor the physical stability of emulsions. Assays of potency and degradant levels are used to monitor the chemical stability of emulsions.

**Particle (droplet) size.** An important parameter is the particle (droplet) size of the emulsion. A variety of instruments and techniques exist for monitoring particle size. The most widely used techniques rely on laser light scattering, as reviewed by Tadros et al. (2004). Instruments manufacturers include Nicomp, Coulter, Horiba, Sympatec, and Malvern. Electron microscopy has also been used, but artifacts introduced by fixing techniques should be carefully controlled. Typically, emulsions produced by the methods described above yield particle sizes of 100–1000 nm; particle sizes less than 200 nm are generally required for emulsions used intravenously.

**Viscosity.** This parameter can be monitored by standard rheological techniques. The rheological properties of emulsions, reviewed by Sherman (1983), can be complex, and depend on the identity of surfactants and oils used, ratio of disperse and continuous phase, particle size, and other factors. Flocculation will generally increase viscosity; thus, monitoring viscosity on storage will be important for assessing shelf-life.

**Osmolarity.** Osmolarity of a conventional emulsion is largely determined by components of the continuous phase, and the disperse phase may contribute little to the osmolarity. Thus, water-soluble excipients such as glycerol are frequently added to adjust tonicity of emulsions intended for parenteral use. Conventional techniques can be used for monitoring osmolarity. Owing to possible changes in emulsion structure on freezing, instruments that rely on vapor pressure lowering are more suitable for monitoring osmolarity of emulsions than those based on freezing point depression.

**Zeta potential.** Zeta or electrokinetic potential is related to the surface charge of the emulsion droplets and it is generally measured by electrophoretic techniques. The zeta potential is highly dependent on the surfactants used. Yamaguchi et al. (1995) compared the properties of otherwise identical 10% soybean oil emulsions prepared from two different sources of lecithin: one containing 99% PC and the other containing only 70% PC, with phosphatidyl ethanolamine (PE) comprising much of the remaining phospholipid. At pH 4, 5, 6, and 8 the purified (99%) lecithin emulsion had zeta potentials of 5, –3, –8, and –30 mV, respectively, reflecting the zwitterionic nature of PC. In contrast, the crude (70%) preparation had zeta potentials of –15, –30, –45, and –60 mV, respectively, at the same pH values, reflecting the ionization properties of the free amino group of the PE (Yamaguchi et al., 1995). A charged drug molecule at the interface will also affect the zeta potential.

**Chemical stability.** Certain emulsion components, especially those derived from unsaturated lipids, can give rise to undesirable degradation products on storage. These can include oxidative products (e.g., lipid hydroperoxides and aldehydes), which may impair drug stability. Figure 10.1 shows a schematic of lipid peroxidation, using a linoleic acid ester (e.g., a glyceride) as an example. The process is quite complex; a variety of pathways can ensue, giving a multitude of products and a number of assays that can be used to monitor lipid peroxidation. Lipid peroxidation is a radical initiated

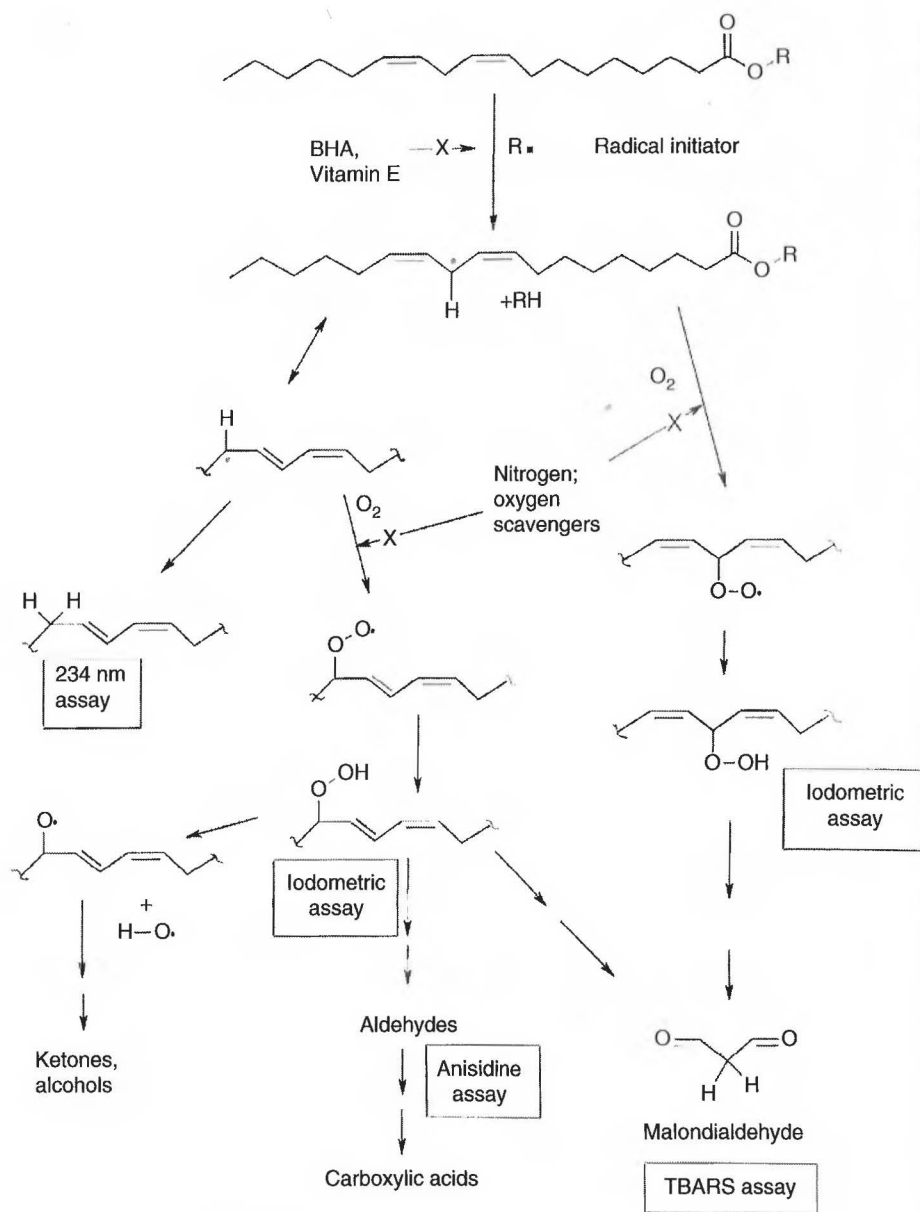


**FIGURE 10.1** Schematic of the mechanisms of lipid peroxidation using a linoleic acid ester as a substrate.

reaction; the radicals can initially arise from trace quantities of metal ions or other impurities, from peroxides present in propylene glycol (PEG)-based surfactants in the formulation, or from exposure to light that can generate singlet oxygen. The methylene group between two  $\alpha, \delta$  diene double bonds (present in linoleic and linolenic acids) is particularly susceptible to abstraction by radicals due to resonance stabilization of the product. The lipid radical initially formed can react with oxygen to give a peroxy radical, propagating the radical pathway by abstracting a hydrogen from unreacted lipids to form a lipid hydroperoxide, which can be measured by an iodometric assay (Porter, 1984). This lipid hydroperoxide can decompose to give malondialdehyde (absorbance at 532 nm) and other products; thiobarbituric acid, which forms a colored product with malondialdehyde, can be used to quantitate these and similar products in the thiobarbituric acid reactive substances (TBARS) assay

(Abuja and Albertini, 2001). Alternatively, and more likely, the initially formed radical from the  $\alpha, \delta$  diene can react through the alternate resonance form to form a conjugated diene, in this case 9-(*cis*)-11-(*trans*)-octadecenoic acid (detectable by its UV absorbance at 230–235 nm) (Antolovich et al., 2002), or react with oxygen to form conjugated lipid hydroperoxides. These can either decompose to give the highly reactive hydroxyl radical (with the remaining lipid fragment giving rise to ketone and alcohol products), or decompose to short-chain aldehydes (e.g., hexanal, butanal), which can be quantitated using the anisidine assay (Antolovich et al., 2002). Aldehydes themselves can be oxidized to short-chain carboxylic acids (e.g., butyric acid). These carbonyl products are responsible for the disagreeable odor associated with rancidity of lipids, and more importantly, can give rise to drug instability.

As shown in the diagram, several different assays have been used in the past to monitor the lipid peroxidation process (Lang and Vigo-Pelfrey, 1993). Because of the complexity of the process, it is difficult to predict the ultimate pathway. Thus, using a single assay to quantitate the extent of lipid peroxidation may not be representative of the overall level of degradation. For example, the TBARS assay is reported to be unspecific and prone to artifacts (Abuja and Albertini, 2001), while the iodometric assay may not be reflective of the overall extent of peroxidation if lipid hydroperoxides do not build up and instead decompose (Antolovich et al., 2002). A method that monitors the overall peroxidation process by measuring the increase in conductivity and the associated induction time is the Rancimat method (Laubli and Bruttel, 1986; Halbaut et al., 1997). If it is suspected that lipid peroxidation could be a problem for drug instability or formulation properties, it may be more meaningful to monitor specific types of agents (e.g., HPLC assay of aldehydes).

More importantly, lipid peroxidation can be controlled or minimized by design of formulation. While saturated lipids (e.g., MCTs) will themselves not be susceptible to peroxidation, they may contain sufficient unsaturated impurities to be problematic. Similarly, monounsaturated lipids (e.g., oleic acid glycerides) are much less susceptible to peroxidation. The relative rates of peroxidation of oleic, linoleic, and linolenic acids are 6:64:100, respectively (Swern, 1995). Monounsaturated lipids may, however, contain polyunsaturated impurities, which will catalyze the oxidation of the monounsaturated components (Swern, 1995). Surfactants, particularly those based on PEG, may contain peroxides that can promote lipid peroxidation; thus, particular attention should be paid to the purity and source of all formulation components.

The other important factor in retarding and controlling lipid peroxidation is the use of appropriate antioxidants, which can inhibit the pathway at various points and stabilize lipids. The most useful are phenol-based antioxidants, for example, butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), propyl gallate, and Vitamin E ( $\alpha$ -tocopherol). All of these form stable free radicals, thus acting as radical scavengers and chain terminators. When using Vitamin E, it is important to remember that only the free phenol is active as an antioxidant; derivatives such as Vitamin E acetate or TPGS will not inhibit lipid peroxidation until metabolized. Other antioxidants (e.g., ascorbic acid, ascorbyl palmitate) act as oxygen scavengers, which will prevent formation of lipid hydroperoxides but not conjugated dienes. The two types of antioxidants, by acting at different points in the pathway, can act synergistically if used together (*Handbook of Pharmaceutical Excipients*, 1994). It should be noted that ascorbic acid derived oxygen scavengers are also reducing agents, and in fact can promote rather than retard peroxidation if metal ions are present (Sevanian and Ursini, 2000); inclusion of a chelating agent such as EDTA in the formulation will prevent this and enhance the antioxidant activity of ascorbates. Use of ascorbates with drugs sensitive to reducing agents should be avoided. Use of a nitrogen atmosphere for formulation manufacture is another, but less convenient, method for excluding oxygen.

Hydrolysis is the other important mechanism for some lipids (glycerides and phosphoglycerides) to degrade. Lowering of pH can arise from both hydrolysis and lipid peroxidation (Arakane et al., 1995), as both processes can give acid products. It has also been reported that hydrolysis and peroxidation can act in synergy with one another in liposome bilayers (Swern, 1995), but it is uncertain whether this can happen for other structures since different mechanisms are operative for

emulsified lipids and bulk lipids (Antolovich et al., 2002). Hydrolytic products (e.g., free fatty acids, mono- and diglycerides, and lyso-phospholipids) can form that can alter the surface properties and zeta potential of the emulsion and distribute into the aqueous phase (Herman and Groves, 1992, 1993). Fatty acid formation can also decrease the pH and increase the conductivity of the emulsion (Santos Magalhaes et al., 1991). Hence, these two parameters should be monitored to aid stability evaluation. The emulsion excipients (namely, oils, surfactants, and cosolvents) should be monitored by periodic assays to insure no loss of excipient concentration.

**Physical stability.** As indicated earlier, conventional emulsions are inherently unstable from a physical standpoint. Poor physical stability is ultimately exhibited by phase separation, which can be visually monitored. Certain properties of the emulsion will start to change long before this separation is visually apparent. An increase in particle size is particularly indicative of physical instability, since this monitors the coalescence or flocculation that is part of the process involved in ultimate phase separation. Increases in viscosity (due to flocculation) and changes in zeta potential (arising from a decrease in droplet surface area) are both indicative of poor physical stability. The presence of drug and cosolvents can potentially hasten the phase separation.

From a theoretical standpoint, physical stability is probably the most complex property of emulsions. The key factor in determining the stability of an emulsion is believed to be the interfacial tension between the two phases, and lower interfacial tension (primarily governed by the surfactant) will increase the stability (Collins-Gold et al., 1990). Very low interfacial tension is thought to be the primary factor leading to the stability of microemulsions. A number of models allowing prediction of the stability of emulsions have been put forth. One of the most useful approaches is the so-called DLVO theory, developed over 50 years ago by Derjaguin and Landau (1941) and Verwey and Overbeek (1948). According to this theory, the stability of an emulsion depends on a balance of electrostatic repulsive forces and London-type Van der Waals attractive forces. Thus, higher surface charge (characterized by high absolute values of the zeta potential) will generally tend to stabilize emulsions due to the higher repulsion of the droplets from one another. For example, a 70% PC emulsion had a higher overall physical stability than a 99% PC emulsion, reflecting the latter's lower surface charge (Yamaguchi et al., 1995). An overabundance of electrolytes will generally tend to destabilize emulsions due to a lowering of the surface charge, leading to a so-called salting out effect, wherein the emulsion will undergo flocculation and phase separation at sufficiently high electrolyte concentration. Calcium and other divalent ions are particularly destabilizing. A parameter can be derived known as the "critical flocculation concentration" (CFC), which is the electrolyte concentration at which flocculation begins. For the PC emulsions described earlier, the CFC's for  $\text{CaCl}_2$  were 0.4 mM for 99% PC and 1.2 mM for 70% PC (Yamaguchi et al., 1995).

## DRUG SOLUBILIZATION AND DELIVERY USING EMULSIONS

### RATIONALE

Various formulation approaches can be used for solubilization and delivery of pharmaceutical compounds. If the compound has ionizable groups, salt formation is often the first strategy used to improve solubility. Otherwise, use of cosolvents is perhaps the most common alternative for solubilization of compounds, probably owing to the high efficiency and ease of use of cosolvents to solubilize drug. However, the use of cosolvents has the potential to cause problems like drug precipitation on dilution, and pain and/or tissue damage on parenteral administration. Emulsion formulations have the potential to avoid precipitation after injection. Other approaches include prodrugs, surfactant (micellar) systems, complexation, and liposomes. Combined approaches of emulsions with one of the other formulation strategies may also be used to advantage. As mentioned

above, cosolvents are frequently used to incorporate drugs into an emulsion. Similarly, use of a lipophilic counterion to increase drug affinity to an emulsion may be considered an approach combining salt formation and emulsion strategies. There have been several reports of lipophilic prodrugs having higher affinity to and retention within the oil phase of an emulsion relative to the parent drug. Incorporation of palmitoyl rhizoxin into an emulsion protected the drug from degradation in plasma (Kurihara et al., 1996). Similar prodrug emulsion examples include a prostaglandin E1 prodrug (Matsuo, 1998), etoposide oleate (Azevedo et al., 2005), and paclitaxel oleate (Rodriguez et al., 2005).

Emulsions are an attractive alternative for drug solubilization. If the drug has moderate solubility in bioacceptable oils, emulsion systems could offer several benefits apart from drug solubilization that are rarely achievable with other formulation systems. Some of these include improvement in drug toxicity, sustained drug release *in vivo*, reduction in pain, irritation and tissue damage after parenteral delivery. For example, emulsion formulation of amphotericin B has been shown to cause significantly less damage to RBCs than the commercial product, Fungizone® (Forster et al., 1988). Emulsions have also been shown to reduce the toxicity of drug (e.g., miconazole) (Levy et al., 1995). Other examples of emulsions for reduction in adverse effects after parenteral dosing will be mentioned in subsequent sections.

Use of an emulsion formulation for pharmaceutical drug delivery generally mandates that the drug be present in the internal (i.e., dispersed) phase and at the interface. This means that the process meets one of the following criteria:

1. Drug has a high log *P* value, that is, the drug prefers to partition into lipophilic versus aqueous media. For example, an *O*-alkyl-*N*-aryl thiocarbamate has poor solubility in water or water containing cosolvents; however, its solubility is 2–3 orders of magnitude higher in oils, expediting emulsion preparation (Strickley and Anderson, 1993).
2. Drug is marginally soluble in oils; however, it can be improved with the aid of excipients. For example, the oil solubility of clarithromycin has been increased with the aid of counterions like hexanoic and oleic acid (Lovell et al., 1994).
3. Drug is soluble in neither oil nor water; however, it can be retained at the interface of an emulsion. Thus, if a liposomal preparation can be made in which the drug resides in the lipid bilayer, or if it can be solubilized into micelles by an appropriate detergent, an emulsion can probably be made wherein the drug resides at the interface.

Conformance to one or more of the above criteria generally qualifies development of an emulsion formulation for drugs that otherwise cannot be successfully administered parenterally as a solution. Hence, emulsions have been explored for improved drug efficacy after oral, topical and parenteral administration, and for improved patient compliance (e.g., reduced pain or irritation after parenteral administration, and improved palatability after oral delivery).

In addition, the formulations should meet the following two requirements:

1. The drug is retained in the dispersed phase or at the interface over time under normal handling and storage conditions.
2. Drug solubilization and delivery using emulsions does not lead to undesirable changes in its chemical stability, efficacy, or toxicity.

Examples of studies supporting use of emulsions for a variety of drug delivery needs are listed in Table 10.4. Some of the advantages conferred by emulsion formulations may be mediated by an improved solubilization of the drug. There is also a growing list of studies suggesting use of emulsions for drug solubilization *per se*; these are summarized in Table 10.5.

**TABLE 10.4**  
**A Representative List of Compounds Tested for Delivery as an Emulsion**

| Rationale for Emulsion Formulation | Compound(s) Tested          | Reference(s)                                                           |
|------------------------------------|-----------------------------|------------------------------------------------------------------------|
| Pain on injection                  | Etomidate                   | Doenicke et al. (1990) <sup>a</sup> ; Kulka et al. (1993) <sup>a</sup> |
|                                    | Diazepam                    | Von Dardel et al. (1983) <sup>a</sup>                                  |
|                                    | Clarithromycin              | Lovell et al. (1994, 1995)                                             |
| Thrombophlebitis                   | Etomidate                   | Doenicke et al. (1990) <sup>a</sup> ; Kulka et al. (1993) <sup>a</sup> |
| Reduced toxicity                   | Cyclosporine                | Tibell et al. (1993); Venkatraman et al. (1990)                        |
|                                    | Amphotericin B              | Forster et al. (1988); Lamb et al. (1991)                              |
|                                    | Vincristine                 | Junping et al. (2003)                                                  |
| Improved stability                 | Sodium phenobarbital        | Dietz et al. (1988)                                                    |
|                                    | Oxathiin carboxanilide      | Oh et al. (1991)                                                       |
|                                    | Physostigmine               | Pathak et al. (1990)                                                   |
|                                    | Perilla ketone (NSC 348407) | Paborji et al. (1988)                                                  |
| Prolonged activity                 | Peptides                    | Gasco et al. (1990)                                                    |
|                                    | Somatotropin                | Tyle and Cady (1990)                                                   |
|                                    | Physostigmine               | Benita et al. (1986)                                                   |
|                                    | Etoposide                   | Reddy and Venkateswarlu (2005)                                         |
| Drug targeting                     | Bleomycin                   | Tanigawa et al. (1987) <sup>a</sup>                                    |
|                                    | Titanocene dichloride       | Muller et al. (1991)                                                   |
|                                    | Mitomycin C                 | Nakamoto et al. (1975)                                                 |
| Vaccine adjuvants                  | Muramyl dipeptide           | Lidgate et al. (1989)                                                  |

<sup>a</sup> Describe clinical studies.

## MECHANISM OF DRUG RELEASE AND DRUG ABSORPTION

On introduction of a drug-containing emulsion into the biological milieu (into plasma by IV administration), drug diffusion out of the emulsion droplet occurs. To some extent, the kinetics of this process are governed by such properties as the distribution coefficient of drug between the emulsion oil phase, interface and external aqueous phase. Yamaguchi et al. (1994) examined the release of PGE1 from an o/w emulsion by equilibrium dialysis, and showed that 93% of the drug diffuses into the buffer, and all but 0.2% of the remainder is located at the interface. The process was suggested to be controlled by Fickian diffusion. In another study, a "reverse dialysis" technique was used to measure the *in vitro* release properties of clofibrate from an emulsion formulation, whereby 1 mL of the emulsion was added to 500 mL of a buffer sink, along with a dialysis sack containing buffer alone (Santos Magalhaes et al., 1991). Measurement of the rate of appearance of drug in the dialysis sack allowed calculation of the kinetics of drug release from the emulsion droplets. The results were comparable to those from an ultrafiltration method utilizing microcentrifuge filters. Both methods were indicated to be superior to standard dialysis techniques (i.e., where the emulsion is placed inside the dialysis sack), because diffusion of drug across the dialysis membrane can be the rate limiting step in standard techniques. Lundberg (1994) monitored leakage of the anticancer drugs etoposide oleate and teniposide oleate from emulsion droplets using gel permeation chromatography.

The quantitation of release of drug from an emulsion in the presence of serum is significantly more complex because of binding of drug and emulsion components to plasma proteins as well as plasma metabolism of emulsion lipids. Phospholipids of Liposyn®/Intralipid®-type emulsions are known to bind to plasma lipoproteins, especially HDL (Williams and Tall, 1988). Minagawa et al. (1994) developed a technique for monitoring release of an antithrombic drug, TEI-9090, from emulsion droplets in serum by incubation of the test emulsion/serum mixtures with polydimethylsiloxane glass beads in the presence of SDS. The latter displaced drug bound to serum albumin.

**TABLE 10.5**  
**A Representative List of Experimental Studies Exploring Emulsion System for Drug Solubilization**

| Drug                                                                   | Reference(s)                                      | Application/Result                                                                                 |
|------------------------------------------------------------------------|---------------------------------------------------|----------------------------------------------------------------------------------------------------|
| Oxathiin carboxanilide (NSC 615985)                                    | Oh et al. (1991)                                  | Solubilization in emulsion for tox studies                                                         |
| Anticancer agent NSC 278214                                            | El Sayed and Repta (1983)                         | Enhanced stability (100-fold) in emulsions relative to aqueous systems                             |
| Hexamethylmelamine                                                     | Ames and Kovach (1982)                            | Emulsion reduces local irritation and venous thrombosis after IV injection                         |
| Etoposide and teniposide derivatives                                   | Lundberg (1994)                                   | Enhanced solubilization, cellular uptake, and cytotoxic activity of lipophilic prodrugs            |
| Penclomedine                                                           | Prankerd et al. (1988)                            | Emulsion formulation was more active and less toxic in mouse tumor model                           |
| Paclitaxel                                                             | Tarr et al. (1987)                                | Triacetin emulsion to solubilize drug, alternative to surfactants, and cosolvents                  |
| Halothane                                                              | Johannesson et al. (1984);<br>Biber et al. (1984) | IV administration of emulsion formulation induced anesthesia similar to inhalation route           |
| Pregnanolone                                                           | Hogskilde et al. (1987a,b)                        | Good anesthetic affect from emulsion, avoids allergic reaction from Cremphor EL                    |
| Rhizoxin (NSC 332598)                                                  | Stella et al. (1988)                              | Solubilization in emulsion formulation for slow infusion                                           |
| Anti-HIV: NSC 629243                                                   | Strickley and Anderson (1993)                     | Emulsion formulation enhanced solubilization and stabilization                                     |
| Testosterone and its esters; progesterone; medroxyprogesterone acetate | Malcolmson and Lawrence (1993)                    | Solubilization of steroids in emulsions; high drug loading achievable depending on $\log P_{o/w}$  |
| Clarithromycin                                                         | Lovell et al. (1994)                              | Emulsion formulation decreased pain on injection                                                   |
| All- <i>trans</i> -retinoic acid (ATRA)                                | Hwang et al. (2004)                               | Emulsion formulation enhanced drug solubilization and stabilization; maintained antitumor activity |
| Prostaglandin: TEI-9826                                                | Fukushima et al. (2000)                           | Emulsion formulation retarded tumor growth in mouse and rat models with sustained infusion         |
| Flurbiprofen                                                           | Park and Kim (1999)                               | Solubilization in emulsion formulation reduces volume required for parenteral delivery             |

and the beads selectively adsorbed the free drug. *In vivo*, the situation is even more complicated because of the tendency of emulsions to be taken up by the phagocytic cells of the reticuloendothelial systems (RES). Phospholipid-oil based emulsions resemble chylomicrons, which are rapidly cleared by liver: 65% of exogenously injected chylomicrons are recovered in the liver within 30 minutes after injection (Van Berkel et al., 1991). Triglycerides are removed and digested by lipoprotein lipases present in capillary endothelium, and the remnant emulsion droplets are almost completely

taken up by the liver within a few hours (Handa et al., 1994). Thus, these factors could have a significant impact on the pharmacokinetics and biodistribution of the drug. If the diffusion of drug from the emulsion is slow, then a high uptake of drug by the RES cells will be expected. This may be desirable in some cases where liver and spleen are the therapeutic targets, and where subsequent slow release of drug from these sites is desirable, and where toxicity of drug to sites of low emulsion uptake would otherwise be a problem. On the other hand, if diffusion of drug out of the emulsion is rapid compared to the metabolism and clearance of the emulsion droplets, then the pharmacokinetics and distribution of the drug will be little different from those of aqueous formulations. In studies using a rat liver perfusion system comparing emulsions with mean diameters of 252nm and 85nm containing [ $^3\text{H}$ ] retinoic acid ( $\log P_{o/w} = 6.6$ ) and [ $^{14}\text{C}$ ] cholesterol oleate (calculated  $\log P_{o/w} = 18$ ), the rates of RES uptake and plasma release were shown to depend on the emulsion size and drug partition coefficient (Takino et al., 1995). It has been suggested that drugs with a  $\log P_{o/w} > 9$  will be retained in the lipid phase regardless of the emulsion's composition and particle size (Kawakami et al., 2000).

On the basis of these considerations, formulation of a drug may or may not have a significant impact on the pharmacokinetic properties of the drug, and there have been a number of studies comparing emulsion and aqueous-based formulations with regard to this question. Cyclosporine (Sandimmune<sup>®</sup>), is normally formulated for IV use with Cremophor EL, a solubilizer, which is known to cause nephrotoxicity. When formulated as a 1.2% phospholipid/10% soybean oil emulsion incorporating 2–3 mg/mL drug, the nephrotoxicity in rats was decreased (Tibell et al., 1993) without changes in systemic clearance, volume of distribution, or elimination half-lives in rats and pigs. Hence the two formulations were considered bioequivalent (Tibell et al., 1995). Another study compared cyclosporine formulated as liposomes and as an emulsion (with 10 mg/mL cyclosporine in 20% Intralipid<sup>®</sup>) with Sandimmune<sup>®</sup>. All three formulations showed similar elimination half-lives, but Sandimmune<sup>®</sup> showed significantly higher AUC values and lower volume of distribution than the other 2 formulations (Venkatraman et al., 1990). The binding of cyclosporine to lipoproteins was suggested as one reason for the differences in the *in vivo* behavior among the formulations. Similar contrasting results have been obtained with diazepam. Earlier reports indicated significantly lower plasma diazepam levels with Diazemuls<sup>®</sup> emulsion than Valium<sup>®</sup> injectable solution (5 mg/mL diazepam in 10% ethanol/40% propylene glycol) (Fee et al., 1984); however, later studies were unable to find a significant difference (Naylor and Burlingham, 1985).

An emulsion formulation of hexamethylmelamine in 20% Intralipid<sup>®</sup> resulted in peak plasma drug concentrations and rates of elimination similar to those from a pH 2–3 aqueous formulation of the hydrochloride salt; however, the emulsion alleviated the vein irritation in rabbits (Ames and Kovach, 1982). This suggests that drug remains associated with the emulsion long enough to reduce local tissue irritation, but diffuses rapidly into serum at sites distal from the injection site. In the case of propofol emulsion (Diprivan<sup>®</sup>), an anesthetic, the drug molecule distributes rapidly from blood to tissues, with a blood-brain equilibration time of only 2–3 min. No difference in pharmacokinetics has been observed between healthy patients and those with liver cirrhosis (Dundee and Clarke, 1989). These observations suggest that the emulsion has little effect on the distribution of propofol, which is not surprising based on the low molecular weight of the drug.

The antifungal drug amphotericin B (AmB) is currently marketed for IV administration as a colloidal dispersion with sodium deoxycholate as a solubilizer (Fungizone<sup>®</sup>). The formulation has hemolytic and nephrotoxic effects that are believed to arise from membrane damaging effects. Hence, alternate formulations (e.g., liposomes) (Lopez-Berestein, 1988; Gates and Pinney, 1993) and emulsions have been actively explored to alleviate these effects. De novo PC/oil AmB emulsions have shown reduced toxicity in cell culture and animal studies (Davis et al., 1987; Kirsch and Ravin, 1987; Forster et al., 1988; Collins-Gold et al., 1990; Lamb et al., 1991). These results imply an altering of the distribution of the drug away from sensitive membranes. The RES uptake of AmB emulsion has been suggested as a possible reason for its therapeutic advantage (Collins-Gold et al., 1990).

In cases where distribution of emulsion to the RES cells is undesirable, strategies similar to those used for extending the circulating half-lives of liposomes by incorporating PEG or sialic acids into the lipid bilayer could be used (Allen et al., 1989; Woodle and Lasic, 1992). "Long-circulating emulsions" have been described by Liu and Liu (1995), wherein a PEG-derivatized phospholipid has been incorporated into the outer layer of an emulsion. At 30 minutes after injection, only 30% of a conventional emulsion remained in the blood with 50% distributed to the liver, compared to 65% in blood and only 15% in liver at the same time point for the PEG-based emulsion. The apparent reason for this difference is the higher surface hydrophilicity, leading to reduced opsonization and phagocytosis by the RES cells (Liu and Liu, 1995). A similar approach has been used to deliver ibuprofen octyl ester in a poloxamer 338/oil emulsion. This emulsion reduced RES uptake compared to a PC/oil emulsion. The higher hydrophilicity of the poloxamer 338 was hypothesized to reduce the uptake of the emulsion by the RES cells (Lee et al., 1995). Use of more hydrophilic oils such as triacetin to increase dissolution has also been proposed as a strategy to decrease RES uptake of emulsions (Tarr et al., 1987). Incorporation of sphingomyelin into the surface of 100 nm emulsions prolonged their circulation (Takino et al., 1994).

There are fewer reports on other parenteral routes of administration of emulsions such as intramuscular, subcutaneous, and intraperitoneal. Water-in-oil and w/o/w emulsions of bleomycin, mytomyacin C, and 5-fluorouracil have been administered by these routes, apparently resulting in increased regional lymphatic uptake, hence the term "lymphotropic emulsions" (Davis et al., 1987). Gasco et al. (1990) developed a w/o emulsion of an LHRH analog; measurements of testosterone levels after intramuscular administration to rats suggested that the formulation led to prolonged release of the drug.

## EXAMPLES OF EMULSION FORMULATIONS OF WATER-INSOLUBLE DRUGS

### Experimental Case Studies

Lipophilic properties of halothane have been utilized for its parenteral delivery through an emulsion formulation. In one study, 0.3 mL of a 5% halothane in fat emulsion (Intralipid®), prepared *de novo* immediately before testing, was injected through the rat tail vein. The emulsion formulation allowed short-lasting (30–100 s), potent analgesia with reduced adverse effects. All major organs of the animals (e.g., lung, kidney, heart, brain and liver) demonstrated normal histology over a 29-day test period after dosing. Although some animals died in this test after dosing the emulsion formulation (probably due to nonoptimized injection rates), this formulation was found to be superior to injections of regular halothane, which has been shown to cause serious damage to the lung tissue (Johannesson et al., 1984).

Cyclosporine (CsA) is a potent immunosuppressant indicated for the prevention of transplanted organs. However, it is known to cause dose-dependent nephrotoxicity when administered in the conventional formulation containing Cremophor EL; this solubilizing agent itself is reported to be nephrotoxic and allergic to some patients. Hence, feasibility of parenteral delivery of CsA as an emulsion with reduced adverse effects has been assessed (Venkatraman et al., 1990). The test formulation was prepared extemporaneously by adding drug to 20% Intralipid® and mixing the contents until the powder was dispersed. Its performance was tested in rabbits and compared with the marketed IV product, Sandimmune®. Whereas the terminal half-life of drug delivered through emulsion formulation was comparable to that of Sandimmune®, some distribution parameters changed as a result of reformulation. The area under the blood drug concentration versus time curve (AUC) was significantly lower with the emulsion formulation than that with Sandimmune® ( $7397 \pm 2223$  vs.  $13075 \pm 224 \mu\text{g}\cdot\text{hr/mL}$ , respectively; mean  $\pm$  SD,  $N = 4$ ) ( $P = 0.002$ ). However, the lower bioavailability of the emulsion was perceived as an advantage because of possible preferential liver distribution, along with lower drug concentrations in blood immediately after dosing. The emulsion formulation demonstrated *in vivo* mean residence time (MRT) of  $462 \pm 173$ , which was almost

twofold higher than that with Sandimmune® ( $214 \pm 17$ ,  $P = 0.029$ ), indicating that the emulsion system may offer improved efficacy over the commercial product. Hence, the emulsion formulation of CsA was shown to alleviate adverse effects associated with Sandimmune® without compromising the efficacy (Venkatraman et al., 1990).

Several compounds are known to cause pain, irritation and local tissue damage following parenteral administration. Some of these compounds are water-insoluble. Although the exact mechanism of these adverse reactions is not well understood, drug solubilization and its encapsulation in oil droplets of o/w emulsion has been hypothesized to reduce the degree of these unacceptable events. For example, the IV administration of the standard diazepam formulation, a 5 mg/mL drug solution in a vehicle composed of 40% propylene glycol, 10% ethanol and water (Valium®) is frequently known to cause pain and venous sequelae (i.e., change in color and/or thickness of injected vein along with erythema, edema, necrosis, and inflammation of the surrounding tissue). In one study, 0.3 mg/kg diazepam was injected through the ear vein of rabbits as a 5 mg/mL o/w emulsion or 5 mg/mL hydroalcoholic solution. The results of the induction of venous sequelae were compared using saline as a negative control. The emulsion was found to cause significant reduction in local tissue reactions as compared to the hydroalcoholic formulation of diazepam ( $P < 0.05$ ) (see Figure 10.2). No statistical difference was observed in local tissue reaction with saline and the emulsion formulation. The scoring results were confirmed pathologically. Overall, the results suggested that avoidance of irritating solubilizing agents in the formulation and minimization of drug precipitation *in vivo* may reduce local tissue reactions (Levy et al., 1989).

To decrease the IV pain on injection of clarithromycin, the feasibility of emulsion formulation was evaluated. A 5 mg/mL emulsion formulation was developed using oleic and hexanoic acids as lipophilic counterions (Lovell et al., 1994). The degree of reduction in pain was assessed using various animal models, for example, mouse scratch test, rat-paw lick test, rabbit ear vein irritation test and rat tail vein irritation test. In the mouse scratch test, pain with 5 mg/mL emulsion formulation was found to be comparable to 1.6 to 2.7 mg/mL drug solution (see Figure 10.3). In the rat paw lick test, only 70% of the animals receiving emulsion were found to respond to pain as opposed to 100% animals responding to pain after the injection of drug solution. The degree of paw lick (i.e., number

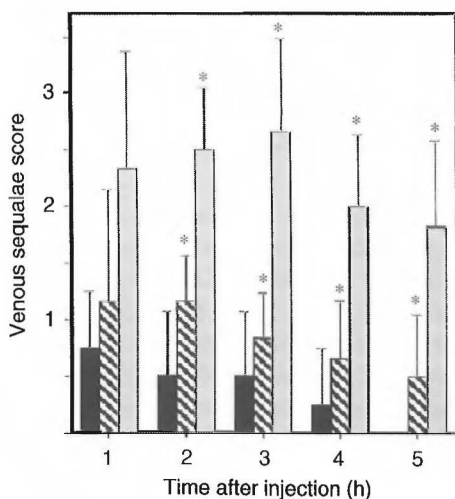


**FIGURE 10.2** Mean venous sequelae scores after IV injection of saline (■), diazepam emulsion (▨), and hydroalcoholic solution of diazepam (□) to rabbits. Bar represents SD of 4–6 animals per group; (\*) indicates significant difference of  $P = 0.05$ . Note the increase in score is indicative of increased severity of inflammation and/or drug reaction. (Adapted from Levy, M.Y., Langermar, L., Gottschalk-Sabag, S., and Benita, S. (1989) *Pharm. Res.*, 6: 510–516. With permission.)

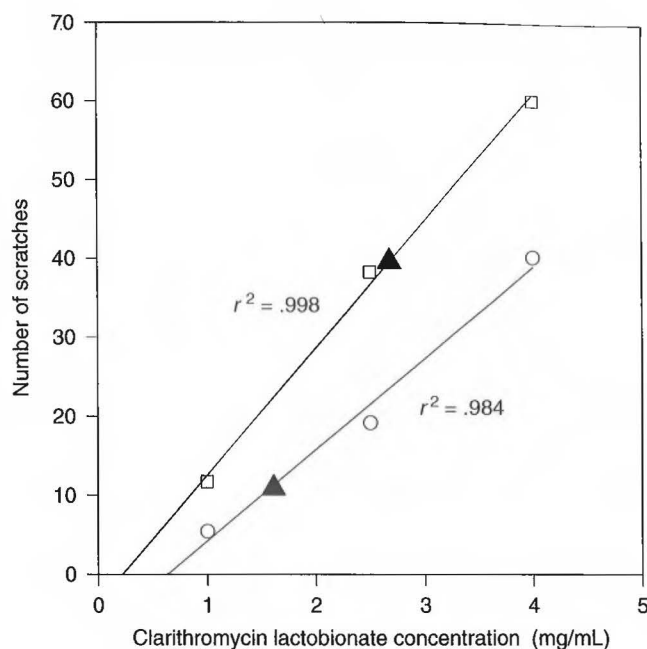


**FIGURE 10.3** Dose response curves in mouse scratch model over the first 5 min (O) and the first 10 min (□) after injection of 1, 2.5, and 4 mg/mL of clarithromycin lactobionate solution to mouse. The scratches with 5 mg/mL clarithromycin are shown by symbol (▲) for comparison. (Adapted from Lovell, M.W., Johnson, H.W., Hui, H.-W., Cannon, J.B., Gupta, P.K., and Hsu, C.C. (1994) *Int. J. Pharm.*, 109: 45–57. With permission.)

of licks per rat and total licking time) was reduced by >50%. In vein irritation tests in rabbits and rats, the extent of adverse reactions at the site of injection was significantly lower with the emulsion than that with the drug solution. In addition, the emulsion formulation did not alter plasma drug distribution, toxicity, and efficacy of the drug (Lovell et al., 1994).

Several studies have examined targeted drug delivery aspects of emulsion formulations. Cancer cells have a much higher expression of LDL receptors on their surface compared to normal cells, and cholesterol-rich emulsions are taken up by these receptors. Uptake levels of paclitaxel oleate delivered in mice through such an emulsion were fourfold higher in tumor tissue than in adjacent normal tissues, and the lethal dose (LD<sub>50</sub>) of the emulsion was ninefold that of the commercial (Cremophor EL) formulation (Rodriguez et al., 2005). Similar results were obtained in animals for cholesterol-rich emulsions delivering daunorubicin (Dorlhiac-Llacer et al., 2001), carmustine (Teixeira et al., 2004), and etoposide (Valduga, 2003). These studies demonstrate the potential of emulsions to increase the therapeutic index of cancer chemotherapeutic agents.

### Clinical Case Studies

Despite immense interest in the use of emulsions for pharmaceutical drug delivery, limited human data has been published with this delivery system beyond the marketed products listed in Table 10.3. In general, following IV administration, emulsion formulations demonstrate plasma profiles similar to those obtained with other solubilized formulations (e.g., micelles and cosolvent systems), but pain on injection or toxicity can be improved. Amphotericin B has been formulated as an emulsion by addition of Fungizone® to Intralipid® 20% and examined clinically. Several reports indicate that the emulsion reduces renal toxicity while maintaining efficacy (Caillot et al., 1992; Chavenet et al., 1992). However, one case report described a patient who had acute renal failure after administration

of amphotericin B emulsion (Alford et al., 1994), perhaps due to incomplete incorporation of the drug into the emulsion droplets and precipitation of drug (Davis, 1995). Pregnanolone (eltanolone) is a water-insoluble anesthetic that has been in clinical trials as an emulsion developed by Kabi Pharmacia, Sweden. In a clinical study, pregnanolone emulsion appears to induce general anesthesia reliably and smoothly in 13 healthy volunteers, with cardiorespiratory effects similar to other anesthetics (Gray et al., 1992). EEG monitoring indicated the dose inducing 50% of the maximal CNS depressant effect to be about 0.57  $\mu\text{g/mL}$  (Hering et al., 1995). In a pharmacokinetic and pharmacodynamic study in 6 volunteers, the elimination half-life of pregnanolone was found to be between 0.9 and 1.4 h; hemodynamics and ventilation were only slightly affected (Carl et al., 1990). Intraiodol<sup>®</sup> is an iodinated lipid emulsion taken up by RES tissues, which has led to its clinical examination in 15 patients as a diagnostic agent for computed tomography (CT) of liver (Ivancev et al., 1989). Similarly, emulsions of perfluorooctyl bromide (perflubron, Imagent<sup>®</sup>) have been developed by Alliance Pharmaceutical Corp. for imaging of liver by both CT and sonography (Behan et al., 1993). They have also been used as contrast agents for lymph node imaging; subcutaneous dosage of perflubron emulsion into the hands of 18 volunteers led to a dose-related enhancement of CT images of axillary lymph nodes (Hanna et al., 1994). A similar perflubron emulsion, Oxygent<sup>®</sup>, has been tested clinically as a temporary oxygen carrier at relatively low (1.35–1.8 g perflubron/kg) doses in 57 conscious volunteers and 30 anesthetized surgical patients (Keipert, 1995). Oxygent<sup>®</sup> can be considered a second-generation analog of Fluosol-DA (Table 10.3). An emulsion formulation of lipophilic prostaglandin E1 prodrug (AS-013) was evaluated in a clinical study with 10 patients with chronic peripheral arterial occlusive disease (PAOD). The stability of the prodrug was improved relative to the parent drug; the emulsion had acceptable efficacy, and no adverse effects were observed (Matsuo, 1998). As indicated in Table 10.4, several studies have examined emulsions in decreasing thrombophlebitis and pain on injection of etomidate and diazepam (Von Dardel et al., 1983; Doenicke et al., 1990; Kulka et al., 1993). Intratumoral injection of a bleomycin emulsion has been used in treatment of cystic hygroma and lymphangioma; results in 27 patients with satisfactory results (Tanigawa et al., 1987).

TOCOSOL<sup>®</sup> Paclitaxel is a tocopherol emulsion formulation of paclitaxel currently in Phase III clinical trial for the treatment of cancers (Constantinides et al., 2004). The tocopherol-based paclitaxel formulation is prepared by dissolving 10 mg/mL paclitaxel in vitamin E and homogenizing with water and surfactants consisting of TPGS and Poloxamer 407 to yield an emulsion with mean particle size of approximately 100 nm. The use of tocopherol reduces the severe adverse effects related to the use of Cremophor EL in Taxol<sup>®</sup> (paclitaxel, Bristol-Myers Squibb). The tocopherol-based paclitaxel formulation can be easily administered to patients in a short 15-min infusion compared to 3-hr infusion required by Taxol. Antitumor activity of the formulation has been demonstrated clinically in bladder, ovarian, and nonsmall cell lung cancers (Hanauske et al., 2005).

An emulsion composed of MCTs with 2% propofol is being developed (Insoluble Drug Delivery-Microdroplet, IDD-D<sup>TM</sup>) as an alternative to the 1% propofol emulsions based on LCTs (e.g., Diprivan<sup>®</sup>) to avoid elevated triglyceride levels normally seen with Diprivan<sup>®</sup>. In a Phase I clinical study, the 2% propofol IDD-D<sup>TM</sup> emulsion had similar propofol plasma concentrations, anesthesia induction times, and anesthesia emergence times to Diprivan<sup>®</sup>. Since MCTs are metabolized more rapidly than LCTs, and since the oil content of the IDD-D<sup>TM</sup> was lower than that of Diprivan<sup>®</sup> (4% vs. 10%), it was concluded that the MCT-based emulsion could avoid the hyperlipidemic effect and bacterial growth common for the LCT-based emulsions (Ward et al., 2002).

A Phase I clinical study was carried out in four ovarian cancer patients to exploit the drug targeting ability of cholesterol-rich emulsions to LDL receptors of tumor cells. Uptake of [<sup>3</sup>H] etoposide oleate and [<sup>14</sup>C] cholesterol oleate were 4.1 times and 4.9 times, respectively, greater than that in contralateral normal ovaries. This indicates that most of the etoposide is retained in the emulsion before its internalization by the tumor cells and shows the ability of the cholesterol-rich emulsions to concentrate in ovarian carcinomas (Azevedo et al., 2005).

## CHALLENGES WITH EMULSION FORMULATIONS FOR DRUG SOLUBILIZATION AND DELIVERY

### PHYSICAL STABILITY

As mentioned earlier, physical stability of an emulsion is perhaps one of the most important characteristics, which governs its commercial success. Being a heterogeneous system, and thermodynamically unstable, this pharmaceutical dosage form has a significantly higher tendency to lose its physical stability than other dosage forms. The assessment of physical stability of disperse systems, including emulsions, is important to allow rejection of unacceptable formulations, provides a basis to estimate long-term stability and expiration dates, allows understanding of mechanism(s) of instability, and provides a basis for setting specifications.

Physical instability of emulsions usually begins with creaming, that is, slow floatation of lipid droplets on more dense aqueous phase, which is usually reversible by shaking. This leads to flocculation and coalescence, that is, aggregation of lipid droplets, which is not reversible by mere agitation. The next stage is creaming of coalesced droplets, which ultimately results in separation of oil and aqueous phases. Owing to this thermodynamic instability, almost all emulsions exhibit increase in droplet size on storage. The extent of this process depends on the characteristics of formulation and its storage condition (see Figure 10.4). Whereas an optimized emulsion formulation may undergo limited change in particle size, a poorly formulated emulsion has a large probability of particle coalescence and irreversible phase separation in a short time. In fact, wherever possible, particle coalescence in emulsion should be minimized as it is known to affect the rate of oral drug absorption and perhaps the efficacy of delivered drug (Toguchi et al., 1990).

Some of the factors that affect the physical stability of emulsions include the type and concentration of surfactant used to stabilize the emulsion, the phase volume ratio (i.e., ratio of oil to aqueous phase), droplet size, compatibility of drug and excipients with the emulsion, and storage condition of the emulsion.

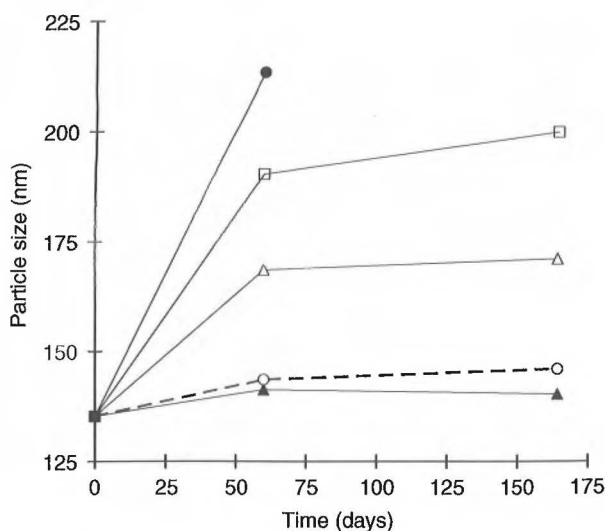


**FIGURE 10.4** Effect of storage temperature on the change in particle size of clarithromycin emulsion over 165 days. The initial pH of the emulsion was 7.5. Key: (▲) 5°C, (○) 30°C, (△) 40°C, (□) 50°C, and (●) 60°C. (Adapted from Lovell, M.W., Johnson, H.W., and Gupta, P.K. (1995) *Int. J. Pharm.*, 118: 47–54. With permission.)

Use of the appropriate emulsifying agent improves the physical stability of an emulsion by one or more of the following mechanisms: reducing interfacial tension, preventing coalescence (by the emulsifying agent being adsorbed around the droplets), imparting electrical potential on the droplets (which favors their repulsion), and/or increasing viscosity (which minimizes droplet interaction). Whereas an inadequate concentration of surfactant will do little to prevent coalescence, undue increase in its concentration often leads to problems like increased drug instability and difficulty in administration. Excess surfactant molecules will tend to self-associate, forming micellar or lamellar structures, which may compromise the effectiveness of the emulsion.

In general, the reduction in the concentration of dispersed phase increases the physical stability of emulsions. Lower dispersed phase concentration translates to a lower number of specific size droplets per unit volume of emulsion. This in turn reduces the degree of droplet interaction, coalescence, and hence phase separation. In general, the dispersed phase concentrations of <40% by volume of total emulsion are acceptable, and <20% desirable.

The compatibility of drug and excipients with emulsion components is important. The chemical properties as well as the amount of excipients can effect their physical stability. For example, increase in drug concentration in the oil phase may seem advantageous from the standpoint of being able to use smaller processing vessels, reduction in dose volume and reduction in the size of packaging commodities; however, increase in drug concentration beyond a certain level may lead to drug precipitation in the surrounding aqueous environment. Hence, the use of counterions to aid dissolution of drug in the oil phase could be evaluated from the standpoint of improving physical stability. Extemporaneous addition of drug to emulsions is also known to induce physical instability (Collins-Gold et al., 1990).

Sudden changes in the storage condition of an emulsion is usually detrimental to its physical stability. Whereas slight changes in temperature may be acceptable, large changes in temperature may cause phase inversion, that is, conversion from o/w to w/o and vice versa. The temperature at which this process occurs is called the phase inversion temperature. Usually, emulsions should be stored at least 20°C below the phase inversion temperature (Attwood and Florence, 1985).

## CHEMICAL STABILITY

Once good physical stability of an emulsion is insured, its commercialization mandates chemical stability of the incorporated drug and other essential components for at least 18 months. Key factors that affect the chemical stability of pharmaceutical emulsions include drug stability in oil, drug stability in aqueous media, drug concentration in oil and emulsion, phase volume ratio, droplet size, presence of excipients, and presence of air and/or peroxide radicals. As mentioned earlier, choice of appropriate antioxidant is important.

Knowledge of the stability of drug in different pharmaceutically approved oils and aqueous media is usually helpful in selecting appropriate formulation ingredients. Differences in the fatty acid composition of various oils can often contribute to different degrees of drug instability. Information on the relative stability of drug in oil versus aqueous media may help make a decision if an emulsion is the preferred dosage form for drug delivery. Implicitly, an emulsion formulation can be developed only if the drug is stable in the oil selected for the emulsion.

Frequently, the hydrophobic environment of the emulsion droplet will retard hydrolysis of susceptible bonds in the drug molecule, gaining a stability advantage over aqueous formulations. For example, formulation of an antineoplastic drug NSC 278214 in a Liposyn® or Intralipid® emulsion rendered the drug about 100-fold more stable than in simple aqueous solution (El Sayed and Repta, 1983). Similar results have been reported by several other workers (Dietz et al., 1988; Paborji et al., 1988; Pathak et al., 1990; Oh et al., 1991). In this situation where the drug is more stable in oil than aqueous media, use of a higher fraction of oil may be advantageous, which translates to a lower drug concentration in oil. This may also improve the physical stability of the formulation, particularly if the drug concentration in oil is close to its solubility limit.

The role of droplet size on drug stability stems from the correlation between droplet size and surface area, and between surface area of droplets and exposure of drug to the aqueous media. If the drug is relatively insensitive to aqueous media, this may not be a major issue; however, for the converse situation, development of emulsions with relatively coarser droplet size may offer improved drug stability. Nonetheless, this should be balanced with physical stability of the emulsion as well as the efficiency of drug absorption after oral administration (Toguchi et al., 1990).

In other cases, however, the presence of certain emulsion components may be problematic for drug stability. In particular, lipid hydroperoxides present in the original lipid and/or surfactant components may destabilize drugs susceptible to oxidative degradation. For example, an anti-HIV drug NSC 629243 containing a thiocarbamate group was oxidatively degraded when formulated in an emulsion owing to the presence of peroxides in the oil. The degradation  $t_{90}$  was found to vary from less than 1 to more than 100 days depending on the age and supplier of the oil (Strickley and Anderson, 1993). Whereas peroxides may not directly interact with drugs, they serve as initiators of the oxidation process. Too low a drug concentration in oil phase may also lead to undesirable levels of drug degradation in the emulsion owing to peroxide triggered oxidation. Hence, emulsion formulations may require addition of oil-soluble antioxidants such as thioglycolic acid (see Figure 10.5) (Strickley and Anderson, 1993). If drug is sensitive to both hydrolytic (aqueous phase) and oxidative (lipid phase) processes, such factors as drug concentration, phase ratio and dose volume may have to be carefully balanced to achieve an optimum formulation.

The extent of pH reduction of emulsions owing to hydrolytic formation of fatty acids depends on the formulation and its storage condition. As can be anticipated, higher storage temperatures will increase the rate of hydrolysis and lead to a greater reduction in pH. While the rate of hydrolysis is generally low at ambient conditions, it could be sufficient to cause 0.05 to 0.08 units decrease in pH per month (see Figure 10.6; Lovell et al., 1995). If the incorporated drug is unusually sensitive to pH changes, the hydrolysis of emulsion should be carefully monitored and, if necessary, controlled by addition of buffer or sodium hydroxide to the initial preparation.

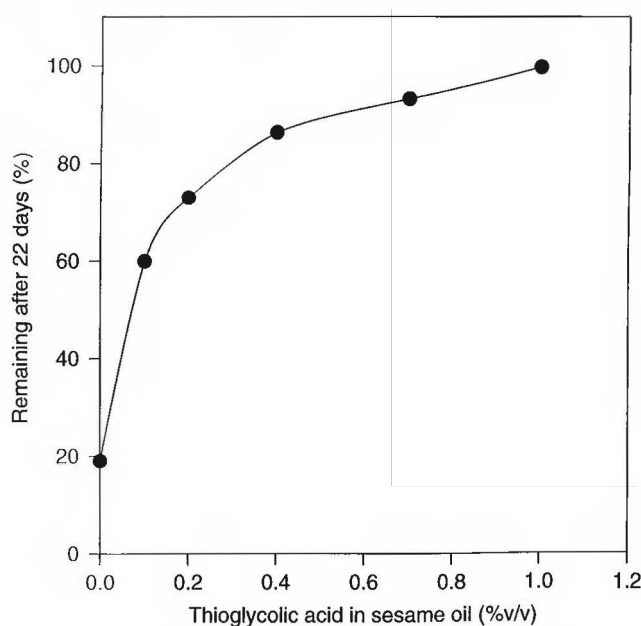


FIGURE 10.5 Effect of thioglycolic acid on the stability of *O*-alkyl *N*-aryl-thiocarbamate in sesame oil at 50°C. (Adapted from Strickley, R.G. and Anderson, B.D. (1993) *Pharm. Res.*, 10: 1076–1082. With permission.)

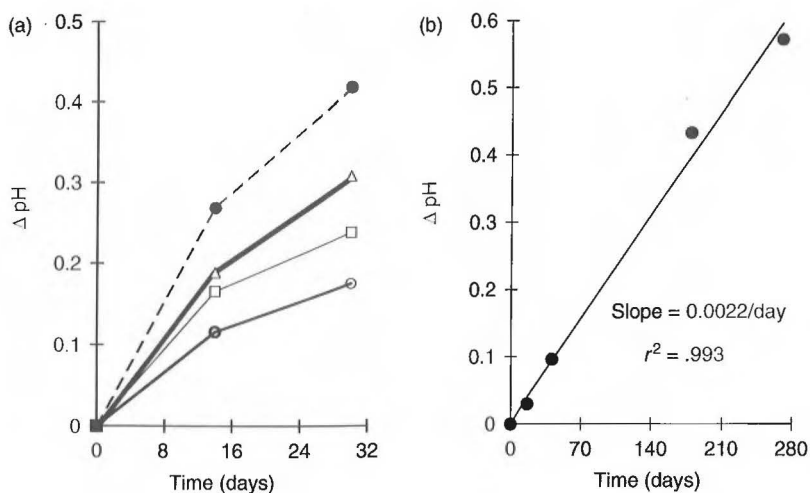


**FIGURE 10.6** (a) Effect of initial pH of clarithromycin emulsion on its pH reduction ( $\Delta\text{pH}$ ) as a function of time at 40°C. Key: (○) pH 6.5, (□) pH 7.0, (Δ) pH 7.5, and (●) pH 8.0. (b) Effect of long-term storage of clarithromycin emulsion on its pH reduction ( $\Delta\text{pH}$ ) at 30°C. The initial pH was 7.5. (Adapted from Lovell, M.W., Johnson, H.W., and Gupta, P.K. (1995) *Int. J. Pharm.*, 118: 47–54. With permission.)

Determination of drug potency in the presence of other emulsion components may require development of special analytical techniques; for example, oils may interfere with standard reverse phase HPLC assays, requiring extraction techniques or the development of normal phase assays. Similarly, bioassays may give erroneous results when the drug is presented in an emulsion form. Hence, adequate controls and/or extraction techniques must be developed to give reliable values from the bioassay.

The assessment of the shelf-life of an emulsion formulation is always a complex issue. Often, the data collected using accelerated conditions does not provide a good estimate of shelf-life because the physical stability of an emulsion may change dramatically with changes in temperature. This alters the relative solubility, partitioning and interaction of drug within the two phases of the emulsion. Sometimes, this can alter the mechanism(s) governing the loss of drug over time. For example, the real-time analysis of clarithromycin o/w emulsion after 1 year at 5°C indicated the presence of 90%–101% drug; however, the shelf-life of this emulsion at 5°C, projected using the data collected at 40–60°C, was found to be much lower than that actually monitored at 5°C (Lovell et al., 1995). Similar complications in the assessment of shelf-life of emulsion formulations has also been reported by other workers (Pathak et al., 1990).

## DOSE VOLUME

As mentioned earlier, the use of emulsions as a dosage form stems from the fact that drugs can be solubilized in oils. However, depending on the dose of drug, intrinsic solubility of drug in oil, physical stability, and chemical stability, an emulsion with limited drug concentration may not be commercially viable especially when an emulsion formulation is intended for subcutaneous (SC) or intramuscular (IM) administration. Ideally, drug concentration in an emulsion will be in the range that is practical for dosing (e.g., dosing volume  $\leq 1$  mL for SC or  $\leq 5$  mL for IM administration). However, for large dose compounds, emulsion formulation may require administration of inconveniently large volumes. Hence, this issue should be kept in mind during the development of this dosage form. For drugs requiring IV dosing, the administration volume is generally a less critical issue.

TOXICITY

If an emulsion formulation utilizes excipients within limits approved for human use, then the toxicity of the formulation is unlikely to be higher than that of the drug. However, if unapproved excipients are used (e.g., to increase drug solubility) or if excipients are used in quantities much larger than those approved for human use, extensive toxicity testings should be carried out before investigation in humans. On the other hand, there may be cases where formulating in an emulsion will decrease toxicity (e.g., cyclosporine and amphotericin B) (Table 10.4).

FORMULATION AND PROCESS OPTIMIZATION

Optimization of an emulsion formulation is perhaps one of the most challenging aspects of its development program. Promising results with preliminary formulations often warrant improvements, for example, with regard to stability, taste, and processing time. However, once a parameter is altered to meet an intended goal, it often leads to loss of some other desirable characteristic. For example, an increase in drug concentration to reduce dose volume may induce physical instability (Davis, 1995). Alternatively, an increase in the oil fraction to aid drug solubilization and/or reduce pain or irritation on injection may also induce physical instability. The complexity of this issue can be appreciated by reviewing the effects of changing some obvious variables as listed in Table 10.6. However, it does not imply that emulsion formulations cannot be optimized. In fact, if formulation optimization is necessary for the life of the development program, it should be pursued using statistical experimental protocols. If chemical stability of drug is critical, then the conclusions regarding reformulated or optimized formulations should be made using the real-time data.

**TABLE 10.6**  
**Probable Effect of Different Variables on the Properties of Emulsion Formulation**

| Variable                             | Probable Effect                                                                                                                                                                                                            |
|--------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Increase in drug concentration       | (a) Physical/chemical instability<br>(b) Increased unpleasant taste<br>(c) Pain/irritation on injection                                                                                                                    |
| Increase in oil concentration        | (a) Increase in particle size and viscosity<br>(b) Difficulty in filter sterilization<br>(c) Physical/chemical instability<br>(d) Increased unpleasant taste<br>(e) Reduced pain/irritation on injection                   |
| Presence of excipients               | (a) Altered physical/chemical stability<br>(b) Altered toxicity                                                                                                                                                            |
| Increase in surfactant concentration | (a) Decrease in particle size<br>(b) Improved physical stability<br>(c) Increased unpleasant taste<br>(d) Increase in pain/irritation on injection<br>(e) Increase in nonemulsion components (namely, micelles, liposomes) |
| Increase in formulation pH           | (a) Improved physical stability<br>(b) Alteration in drug solubility in oil<br>(c) Alteration in chemical stability<br>(d) Increased container/closure incompatibility                                                     |
| Increase in processing temperature   | (a) Decrease in particle size and viscosity<br>(b) Improved drug solubility in oil<br>(c) Increased probability of drug degradation<br>(d) Increased likelihood of drug precipitation on cooling                           |
| Increase in processing pressure      | (a) Narrower particle size distribution<br>(b) Increased probability of drug degradation                                                                                                                                   |

It should be realized that if emulsions are used strictly to solubilize drug, the use of this formulation approach brings the following challenges:

1. Their use as a delivery system may change the biodistribution of parenterally administered drug. Emulsion systems have indeed been investigated for preferential drug localization and altered *in vivo* distribution after parenteral administration (see Table 10.4). The kinetics of efflux from the emulsion droplets and binding to plasma proteins versus uptake by the reticuloendothelial systems should be understood.
2. Their use as an injectable warrants assurance of product sterility. Whereas the FDA-preferred heat-sterilization process is acceptable for total parenteral nutritional (TPN) emulsions, it could affect chemical as well as physical stability of emulsions containing therapeutic agents. Recently, data supporting the filter sterilization of emulsions have been published.
3. The manufacturing process of emulsions is apparently more cumbersome and time-consuming than that for the conventional formulations. This adds to the cost of the product.
4. To maintain good physical and chemical stability, emulsion formulations may warrant storage at 5°C. This limits the manufacturing volume as well as product storage in distribution centers.

At times, extemporaneous addition of drug to a ready-to-use emulsion (e.g., Liposyn®), may not be the preferred way of developing formulations. This can be explained in view of the following reasons:

1. It may require use of an organic solvent. For example, drug is often solubilized in pure cosolvent (e.g., ethanol, dimethylsulfoxide, dimethylacetamide, or N-methyl pyrrolidone) which is then added to the emulsion. As mentioned earlier, this bears toxicological/safety concerns.
2. Extemporaneous addition of drug, alone and/or in solvent, has the tendency to damage emulsion droplets, sometimes resulting in permanent loss of its physical stability.
3. Incomplete solubilization or reprecipitation of extemporaneously added drug cannot be easily ruled out.
4. This process has a tendency to compromise the sterility of the emulsion.

Hence, wherever possible, *de novo* emulsification of oil containing drug is the method of choice for the preparation of drug emulsions.

## FUTURE PERSPECTIVES

As can be appreciated from the review of the literature covered in this chapter, emulsion formulations offer an appealing alternative for the administration of water-insoluble compounds. From the development scientists' standpoint, drug dose and physical stability of formulation in the presence of drug represent the two most challenging aspects of this drug delivery technology. However, these complications are usually compensated by the effectiveness of emulsion formulations for drug solubilization, improved chemical stability, and improved bioavailability. For parenteral applications, an additional benefit may be improved patient acceptance arising from reduced adverse effects (such as pain or irritation).

Owing to the growing number of water-insoluble drugs coming from drug discovery programs, the scope of pharmaceutical emulsions is likely to grow in the future. This is likely to stimulate development of newer "oil-like" synthetic liquids and emulsifying agents. In addition, the industry

will continue to improve techniques for efficient commercial production of these formulations. Overall, these changes will result in greater choices for the development of emulsion formulations of difficult compounds, with perhaps fewer drug solubility and physical stability problems currently encountered owing to limited choice of excipients. Another promising avenue for future development is the use of emulsions for targeted drug delivery, as demonstrated by the potential of cholesterol-rich emulsions to be taken up by LDL receptors of cancer cells (Azevedo et al., 2005); monoclonal antibodies and other targeting moieties can also be explored. Further investigation of long-circulating emulsions derivatized by PEG (Liu and Liu, 1995) or sphingomyelin (Takino et al., 1994) is also warranted to extend the utility of emulsions for drug delivery.

**Table of Registered Trademarks**

| Name                            | Company                                                        |
|---------------------------------|----------------------------------------------------------------|
| Intralipid®; Vitalipid®         | Kabi Vitrum, Stockholm, Sweden                                 |
| Valium®                         | Roche Laboratories Inc., Nutley, New Jersey                    |
| Diprivan®                       | Astra Zeneca, Wilmington Delaware                              |
| Taxol®; Fungizone®              | Bristol-Myers Squibb, Princeton, New Jersey                    |
| Liposyn®                        | Hospira, Lake Forest, Illinois                                 |
| Gaulin®; Rannie®                | Invensys APV, Denmark                                          |
| Microfluidizer®                 | Microfluidics, Newton Massachusetts                            |
| Five Star®                      | Five Star Technologies, Cleveland, Ohio                        |
| Captex®                         | Abitec Corp, Columbus, Ohio                                    |
| Cremophor®; Solutol®; Pluronic® | BASF, Mount Olive, New Jersey                                  |
| Imwitor®; Miglyol®              | Sasol North America Inc., Houston, Texas                       |
| SPAN®; Tween®                   | Uniqema North America Inc., Chicago, Illinois                  |
| Neobee®                         | Stepan Company, Northfield, Illinois                           |
| Sandimmune®                     | Novartis Pharmaceuticals Corporation, East Hanover, New Jersey |
| Phospholipon®                   | American Lecithin Company, Oxford, Connecticut                 |

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