Pharmaceutical Research, Vol. 21, No. 2, February 2004 (© 2004)

Review Article

Solubilizing Excipients in Oral and Injectable Formulations

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Received June 10, 2003; accepted November 5, 2003

A review of commercially available oral and injectable solution formulations reveals that the solubilizing excipients include **water-soluble organic solvents** (polyethylene glycol 300, polyethylene glycol 400, ethanol, propylene glycol, glycerin, *N*-methyl-2-pyrrolidone, dimethylacetamide, and dimethylsulfoxide), **non-ionic surfactants** (Cremophor EL, Cremophor RH 40, Cremophor RH 60, *d*-α-tocopherol polyethylene glycol 1000 succinate, polysorbate 20, polysorbate 80, Solutol HS 15, sorbitan monooleate, poloxamer 407, Labrafil M-1944CS, Labrafil M-2125CS, Labrasol, Gellucire 44/14, Softigen 767, and mono- and di-fatty acid esters of PEG 300, 400, or 1750), **water-insoluble lipids** (castor oil, corn oil, cottonseed oil, olive oil, peanut oil, peppermint oil, safflower oil, sesame oil, soybean oil, hydrogenated vegetable oils, hydrogenated soybean oil, and medium-chain triglycerides of coconut oil and palm seed oil), **organic liquids/semi-solids** (beeswax, *d*-α-tocopherol, oleic acid, medium-chain mono- and diglycerides), various **cyclodextrins** (α-cyclodextrin, β-cyclodextrin, hydroxypropyl-β-cyclodextrin, and sulfobutylether-β-cyclodextrin), and **phospholipids** (hydrogenated soy phosphatidylcholine, distearoylphosphatidylglycerol, L-α-dimyristoylphosphatidylcholine, L-α-dimyristoylphosphatidylglycerol). The chemical techniques to solubilize water-insoluble drugs for oral and injection administration include pH adjustment, cosolvents, complexation, microemulsions, self-emulsifying drug delivery systems, micelles, liposomes, and emulsions.

KEY WORDS: excipients; oral formulations; parenteral formulations; solubilization.

INTRODUCTION

The excipients used to solubilize drugs in oral and injectable dosage forms include pH modifiers, water-soluble organic solvents, surfactants, water-insoluble organic solvents, medium-chain triglycerides, long-chain triglycerides, cyclodextrins, and phospholipids. This review focuses on the solubilizing excipients in commercially available pharmaceutical solution formulations. The published information on oral formulations includes only the list of excipients (1–3), whereas the published information on injectable formulations includes the exact amounts of the excipients (2–10). Two key aspects of any successful solution formulation are solubility and stability. The solvent system chosen must also be able to solubilize the drug at the desired concentration and must provide an environment where the drug has sufficient chemical stability. Sufficient stability is normally defined as <5–10% degradation over 2 years under the specified storage conditions, but the topic of stability (11) is beyond the scope of this review.

THEORY

Solubility at constant temperature and pressure involves the free energy of the solid ($G\text{solid}_{T,P}$) and the free energy of the molecules in solution ($G\text{solution}_{T,P}$). The free energy of a specific solid is fixed (i.e., a property of that solid), but the free energy of the molecules in solution is a function of the solvent and the solution concentration (N). When the solution free energy is less than the solid free energy, molecules will dissolve from the solid until the free energy of the molecules in solution equals the free energy of the solid. At saturation equilibrium solubility, the free energy of the solid equals the free energy of the molecules in solution, Eq. (1).

$$G\text{solid}_{T,P} = G\text{solution}_{T,P}\,(N_{\text{saturation}}) \qquad [1]$$

An increase in solubility at constant temperature and pressure can occur by increasing the free energy of the solid either by chemical means such as varying the salt form or by physical means such as creating an amorphous solid, polymorphs, or particle size reduction (i.e., micronization or nanoparticles). However, the increase in equilibrium solubility via solid-state alterations is only maintained if the solid phase at equilibrium remains the same as the initial solid. Thus, solubility manipulation via solid-state properties is inherently

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ABBREVIATIONS: BHA, butylated hydroxy anisole; BHT, butylated hydroxytoluene; D5W, 5% dextrose in water; DMPC, L-α-dimyristoylphosphatidylcholine; DMPG, L-α-dimyristoylphosphatidylglycerol; DSPG, distearoylphosphatidylglycerol; EDTA, ethylenediaminetetraacetic acid; HP-β-CD, hydroxypropyl-β-cyclodextrin; HSPC, hydrogenated soy phosphatidylcholine; IM, intramuscular; IV, intravenous; LP, lyophilized powder; PEG, polyethylene glycol; PG, propylene glycol; SAIB, sucrose acetate isobutyrate; SBE-β-CD, sulfobutylether-β-cyclodextrin; SC, subcutaneous; SCS, sodium cholesteryl sulfate; SEEDS, self-emulsifying drug delivery system; TPGS, (*d*-α tocopheryl polyethylene glycol 1000 succinate); TRIS, tris(hydroxymethyl)aminomethane; WFI, water for injection.

0724-8741/04/0200-0201/0 © 2004 Plenum Publishing Corporation

more difficult to achieve and to reproducibly control than is alteration of the solution properties.

A more common and controlled means to increase solubility is by decreasing the chemical potential of the molecule in solution, $\mu_{solution}$, by the appropriate choice of solubilizing excipient(s). Chemical potential is the incremental increase in the free energy of a molecule in solution per incremental increase in the number of molecules in solution, Eq. (2). Excipients that solubilize a molecule via bulk solution properties provide a solution environment in which the chemical potential of the molecule in solution is reduced, thereby requiring a higher solution concentration (i.e., solubility) to reach a solution free energy that matches the solid free energy, Eq. (3).

$$\mu_{solution} = (dG_{solution}/dN_{solution})_{T,P} \quad [2]$$

$$dG_{saturated\ solution} = (\mu_{solution})(\text{Solubility}) \quad [3]$$

Excipients that solubilize a molecule via specific interactions such as complexation interact with the molecule in a noncovalent manner that lowers the chemical potential of the molecules in solution. These noncovalent bulk and specific solubility-enhancing interactions are the basis of the phenomenon that "like dissolves like" and include van der Waals forces, hydrogen bonding, dipole–dipole and ion–dipole interactions, and in certain cases favorable electromagnetic interactions.

If the molecule is ionizable, then pH adjustment can be used to increase water solubility because the ionized molecular species has higher water solubility than its neutral species. Equations (4) and (5) show that the total solubility, S_T, is a function of the intrinsic solubility, S_o, and the difference between the molecule's pK_a and the solution pH. The intrinsic solubility is the solubility of the neutral molecular species. Weak acids can be solubilized at pHs above their acidic pK_a, and weak bases can be solubilized at pHs below their basic pK_a. For every pH unit away from the pK_a, the weak acid/base solubility increases 10-fold. Thus, solubility enhancements of >1000-fold above the intrinsic solubility can be achieved as long as the formulation pH is at least 3 U away from the pK_a. Adjusting solution pH is the simplest and most common method to increase water solubility in injectable products (5–10), but is not a major focus of this review because the excipients used to alter the solution pH are commonly used buffers (5–8).

$$\text{For a weak acid} \qquad S_T = S_o\,(1 + 10^{pH\text{-}pK_a}) \quad [4]$$

$$\text{For a weak base} \qquad S_T = S_o\,(1 + 10^{pK_a\text{-}pH}) \quad [5]$$

Cosolvents are mixtures of miscible solvents and are often used to solubilize water-insoluble drugs. Molecules with no ionizable group(s) cannot be solubilized by pH adjustment, and thus a cosolvent approach is often used. Solubility typically increases logarithmically with a linear increase in the fraction of organic solvent(s) as illustrated in Eq. (6). If the cosolvent is composed of one organic solvent and water (i.e., a binary mixture), the solubility can be empirically described as in Eq. (6) by assuming that the total free energy of the system is equal to the sum of the free energy of the individual components (12),

$$\log S_m = f\log S_c + (1 - f)\log S_w \quad [6]$$

where S_m is the total solubility in the cosolvent mixture, S_c is the solubility in pure organic solvent, S_w is the solubility in water, and f is the fraction of organic solvent in the cosolvent mixture. Equation (6) can be simplified to Eq. (7):

$$\log S_m = \log S_w + f\sigma \quad [7]$$

where

$$\sigma = \log ac_w - \log ac_c \quad [8]$$

and ac_w and ac_c are the activity coefficients of the molecule in water and solvent, respectively. The parameter, σ, which is slope of the plot of log S_m vs. f, can be used as a measure of the solubilization potential of a given cosolvent.

If the cosolvent mixture contains more than two organic solvents (i.e., a ternary or higher cosolvent mixture such as a microemulsion) the total drug solubility can be approximated by a summation of solubilization potentials as in Eqs. (9) and (10):

$$\log (S_m/S_w) = \sum (f_i\sigma_i) \quad [9]$$

$$\log S_m = \log S_w + \sum (f_i\sigma_i) \quad [10]$$

Complexation between a ligand and a complexing agent can increase the ligand's solubility if both the ligand and complexing agent have the proper size, lipophilicity, and charge that allow for favorable solubility-enhancing noncovalent interactions. If the ligand and complexing agent combine to form a 1:1 complex, the total ligand solubility, S_T, can be described by Eq. (11),

$$S_T = S_o + K_{11}S_oL_T/(1 + K_{11}S_o) \quad [11]$$

where S_o is the ligand solubility in water, K_{11} is the formation constant of the 1:1 complex, and L_T is the total concentration of the complexing agent (ligand) (13). Thus, the total ligand solubility is a linear function of the concentration of the complexing agent. Using cyclodextrins as complexing agents, solubility enhancements as high as 10^4 to 10^5 can be achieved.

Emulsions are a mixture of water, oil, surfactant, and other excipients. If a water-insoluble molecule is soluble in oil, then it can be solubilized in an emulsion where it partitions into the oil phase. The total solubility in an emulsion, S_{Te}, is the summation of concentrations in the aqueous and oil phases (14). The concentration in the aqueous phase is the solubility in that aqueous phase, S_A, and the concentration in the oil phase can be approximated by the product of the molecule's solubility in the pure oil, S_{oil}, multiplied by the fraction of the oil in the emulsion, f_{oil}, as described in Eq. (12):

$$S_{Te,} = S_A + (S_{oil})(f_{oil,}) \quad [12]$$

ORAL FORMULATIONS

The vast majority of commercially available oral formulations are solid dosage forms such as tablets or capsules, but there are many solubilized oral formulations such as oral solutions, syrups, elixirs, or solutions filled into soft or hard capsules. The reasons for pursuing a solubilized oral formulation include enhancing the oral bioavailability of a poorly water-soluble molecule, a measurable formulation for dose modification, a formulation for patients who cannot swallow tablets or capsules, or a solution for a sore throat/cold remedy. Table I is a list of selected, commercially available solubilized oral formulations arranged alphabetically by drug

Table I. List of Selected Commercially Available Solubilized Formulations for Oral Administration

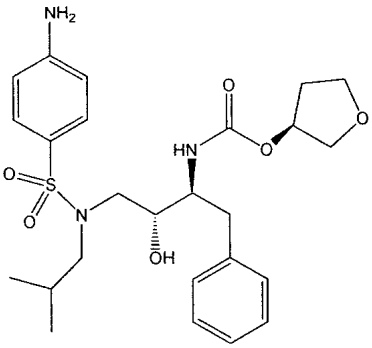
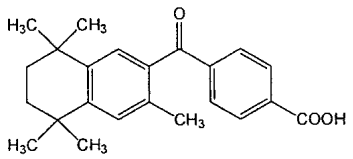
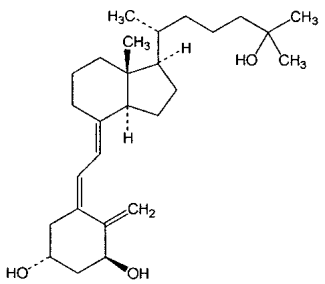
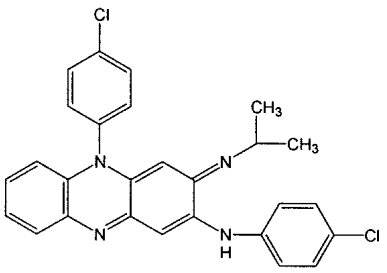
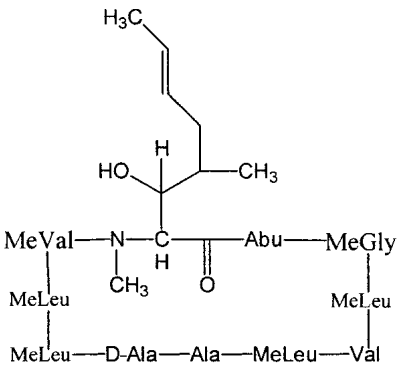
Molecule/ Trade Name/ Company/ Indication	Chemical structure	Water solubility	Commercial oral formulation	Excipients
Amprenavir/ Agenerase/ Glaxo SmithKline/ HIV		36 μg/ml (34)	1. Soft gelatin capsule 50, 150 mg 2. Oral solution 15 mg/ml Oral bioavailability from the solution is 13% less than the capsules (21)	1. TPGS (280 mg in the 150 mg capsule) PEG 400 (247, 740 mg) Propylene glycol (19, 57 mg) 2. TPGS (~12%) PEG 400 (~17%) Propylene glycol (~55%) Sodium chloride Sodium citrate Citric acid Flavors/sweeteners
Bexarotene/ Targretin/ Ligand/ Antineoplastic		Insoluble in water (2)	Soft gelatin capsule 75 mg	PEG 400 Polysorbate 20 Povidone BHA
Calcitrol/ Rocaltrol/ Roche/ Calcium regulator		Relatively insoluble in water (2)	1. Soft gelatin capsule 0.25, 0.5 μg 2. Oral solution 1 μg/ml	1. Fractionated triglyceride of coconut oil (medium-chain triglyceride) 2. Fractionated triglyceride of palm seed oil (medium-chain triglyceride)
Clofazimine/ Lamprene/ Geigy (1960)/ Antileprosy		Virtually insoluble in water (3)	Soft gelatin capsule 50 mg	Beeswax Plant oils Propylene glycol
Cyclosporin A/ I. Neoral/ Novartis/ Immunosuppressant, prophylaxis for organ transplant rejection	 $C_{62}H_{117}N_{11}O_{12}$, MW = 1202.64	Slightly soluble in water (23)	1. Soft gelatin capsule 25, 100 mg 2. Oral solution 100 mg/ml "immediately forms a microemulsion in an aqueous environment" (2) Oral bioavailability is 20–50% (2)	1. Ethanol 11.9% Corn oil-mono-di--triglycerides Polyoxyl 40 hydrogenated castor oil (Cremophor RH 40) Glycerol Propylene glycol *dl*-α-tocopherol 2. Ethanol 11.9% Corn oil-mono-di-triglycerides Polyoxyl 40 hydrogenated castor oil (Cremophor RH 40) *dl*-α-tocopherol Propylene glycol

Table I. Continued

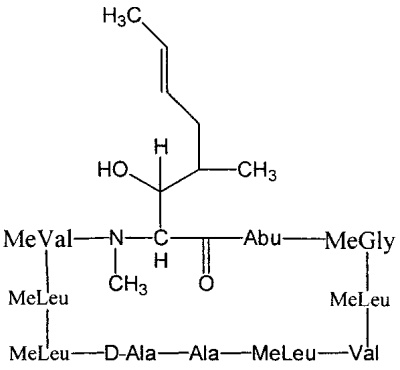
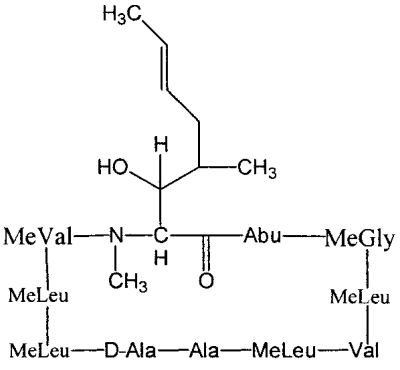
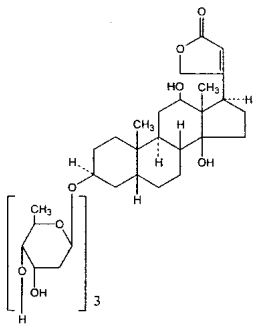
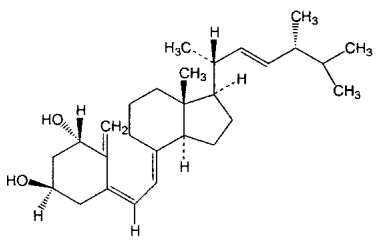
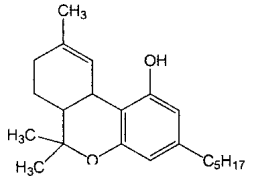
Molecule/ Trade Name/ Company/ Indication	Chemical structure	Water solubility	Commercial oral formulation	Excipients
Cyclosporin A/ II. Sandimmune/ Novartis/ Immunosuppressant, prophylaxis for organ transplant rejection	 $C_{62}H_{117}N_{11}O_{12}$, MW = 1202.64		1. Soft gelatin capsule 25, 50, 100 mg 2. Oral solution 100 mg/ml Oral bioavailability is <10–89% (2)	1. Ethanol 12.7% Corn oil Glycerol Polyoxyethylated glycerides (Labrafil M-2125CS) 2. Ethanol 12.5% Olive oil Polyoxyethylated oleic glycerides (Labrafil M-1944CS) Further dilute with milk, chocolate milk, or orange juice before use.
Cyclosporin A/ III. Gengraf/ Abbott/ Immunosuppressant, prophylaxis for organ transplant rejection	 $C_{62}H_{117}N_{11}O_{12}$, MW = 1202.64		Hard gelatin capsule 25, 100 mg "forms an aqueous dispersion in an aqueous environment", Orally bioequivalent to Neoral (2)	Ethanol 12.8% Polyethylene glycol Polyoxyl 35 castor oil (Cremophor EL) Polysorbate 80 Propylene glycol Sorbitan monooleate
Digoxin/Lanoxin/ Glaxo SmithKline/ Treatment of mild to moderate heart failure		Practically insoluble in water (2)	1. Soft gelatin capsule 50, 100, 200 μg Oral bioavailability is 90–100% (21) 2. Elixir pediatric 50 μg/ml Oral bioavailability is 70–85% (21)	1. PEG 400 Ethanol 8% Propylene glycol 2. Ethanol 10% Methyl paraben 0.1% Citric acid Flavor Propylene glycol Sodium phosphate Sucrose
Doxercalciferol/ Hectorol/ Bone Care/ Management of secondary hyperparathyroidism associated with chronic renal dialysis		Relatively insoluble in water (2)	Soft gelatin capsule 2.5 μg	BHA Ethanol Fractionated triglyceride of coconut oil (medium-chain triglyceride)
Dronabinol/ Marinol/ Roxane and Unimed/ Anorexia or nausea	 pK_a = 10.6	Insoluble in water, is an oil at room temperature. (2)	Soft gelatin capsule 2.5, 5, 10 mg Absorbed 90–95% but oral bioavailability is 10–20% (21)	Sesame oil

Table I. Continued

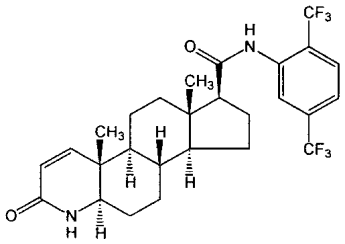
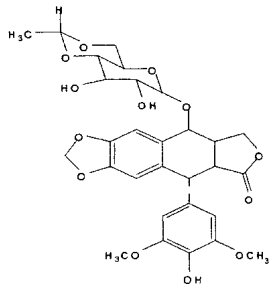
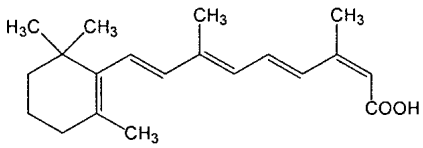
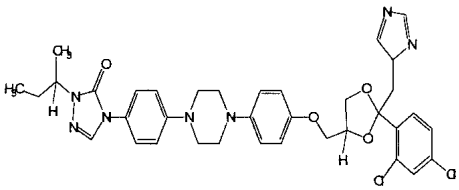
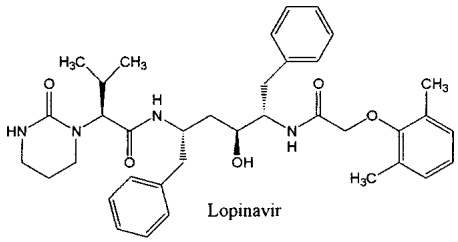
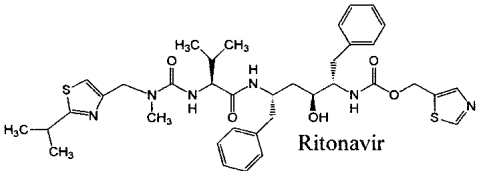
Molecule/ Trade Name/ Company/ Indication	Chemical structure	Water solubility	Commercial oral formulation	Excipients
Dutasteride/ Avodart/ Glaxo SmithKline/ Treatment of benign prostrate hyperplasia		Insoluble in water (Ref. 3, product insert, www.rxlist.com)	1. Soft gelatin capsule 0.5 mg Oral bioavailability is 40–94% (2)	Mixture of mono- and diglycerides of caprylic/capric acid BHT
Etoposide/ VePesid/ Bristol-Myers-Squibb/ Antineoplastic		Sparingly soluble in water (2)	Soft gelatin capsule 50 mg Oral bioavailability is 25–75% (2)	Citric acid Glycerin Water PEG 400
Isotretinoin/ Accutane/ Roche/ Antiachne			Soft gelatin capsule 10, 20, 40 mg	Beeswax BHA EDTA Hydrogenated soybean oil flakes Hydrogenated vegetable oils Soybean oil
Itraconazole/ Sporanox/ Ortho Biotech and Janssen/ Antifungal	 pK_a =3.7	Insoluble in water (2)	Oral solution 10 mg/ml pH2	Water HP-β-CD 40% Propylene glycol 2.5% Sodium saccharin Sorbitol Flavors
Lopinavir and Ritonavir/ Kaletra/ Abbott/ HIV	 Lopinavir  Ritonavir		1. Soft gelatin capsule 133.3 mg lopinavir and 33.3 mg ritonavir 2. Oral solution 80 mg/ml lopinavir and 20 mg/ml ritonavir	1. Oleic acid Polyoxyl 35 castor oil (Cremophor EL) Propylene glycol 2. Alcohol (42.2% v/v) Glycerin Polyoxyl 40 hydrogenated castor oil (Cremophor RH 40) Propylene glycol Sodium chloride Sodium citrate/ citric acid Water Flavors/sweeteners

Table I. Continued

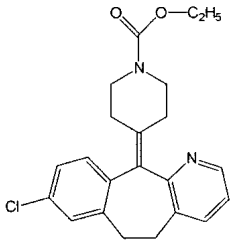
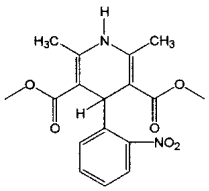
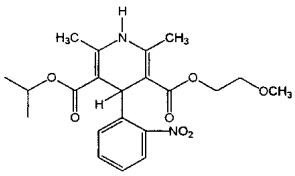
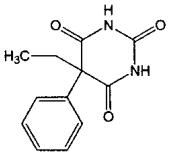
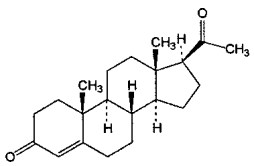
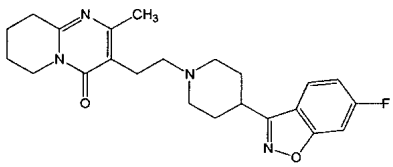
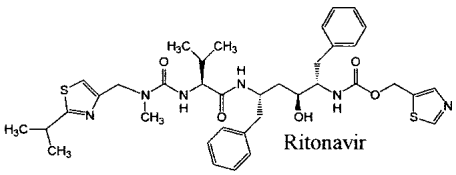
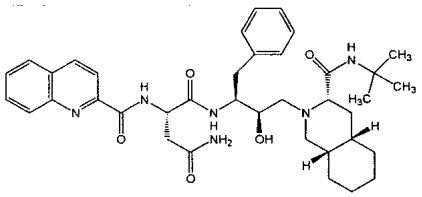
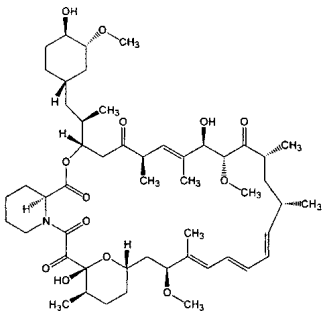
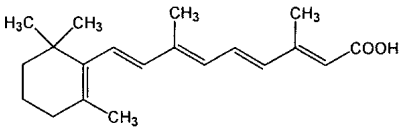
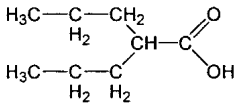
Molecule/ Trade Name/ Company/ Indication	Chemical structure	Water solubility	Commercial oral formulation	Excipients
Loratadine Claratin/ Schering/ Relief of allergies		Not soluble in water (2)	Syrup 1 mg/ml pH 2.5–3.1	Citric acid EDTA Flavor Glycerin Propylene glycol Sodium benzoate Sugar Water
Nifedipine/ Procardia/ Pfizer/ Antianginal		Practically insoluble in water (2)	Soft gelatin capsule 10, 20 mg	Glycerin Peppermint oil PEG 400 Sodium saccharin
Nimodipine/ Nimotop/ Bayer/ Vasodilator		Practically insoluble in water (2)	Soft gelatin capsule 30 mg	Glycerin Peppermint oil PEG 400
Phenobarbital/ Donnatal/ A.H. Robbins/ Anticonvulsant and sedative		1 mg/ml	Elixir 3.5 mg/ml	Ethanol 23% Glucose Sodium saccharin Water
Progesterone/ Prometrium/ Solvay/ Hormone		Practically insoluble in water (2)	Soft gelatin capsule 100 mg micronized	Peanut oil
Risperidone/ Resperdal/ Janssen/ Antipsychotic		Practically insoluble in water, free soluble in 0.1 N HCl (2)	Oral solution 1 mg/ml	Tartaric acid Benzoic acid Sodium hydroxide Water
Ritonavir/ Norvir/ Abbott/ HIV	 Ritonavir pK_a 1.8, 2.6	Intrinsic solubility is 1.0 μg/ml, but the solubility increases to 400 μg/ml at pH 1 at 37°C, upon protonation of the thiazole groups (13)	1. Soft gelatin capsule 100 mg 2. Oral solution 80 mg/ml	1. BHT Ethanol Oleic acid Polyoxyl 35 castor oil (Cremophor EL) 2. Ethanol Water Polyoxyl 35 castor oil (Cremophor EL) Propylene glycol Citric acid Flavors/sweetener/dye

Table I. Continued

Molecule/ Trade Name/ Company/ Indication	Chemical structure	Water solubility	Commercial oral formulation	Excipients
Saquinavir/ Fortovase/ Roche/ HIV (protease inhibitor)		Insoluble in aqueous medium (2)	Soft gelatin capsule 200 mg	Medium-chain mono- and di-glycerides Povidone *dl*-α-tocopherol
Sirolimus/ Rapamune/ Wyeth-Ayerst/ Immunosuppressant		Insoluble in water (2)	Oral solution 1 mg/ml Bioavailability = 14% (2)	Phosal 50 PG (Phosphatidylcholine Propylene glycol Mono- and diglycerides Ethanol 1.5–2.5% Soy fatty acids Ascorbyl palmitate) Polysorbate 80
Tretinoin/ Vesanoid/ Roche/ Antineoplastic			Soft gelatin capsule 10 mg	Beeswax BHA EDTA Hydrogenated soybean oil flakes Hydrogenated vegetable oils Soybean oil
Valproic acid/ Depakene/ Abbott/ Antiepileptic		Slightly soluble in water (1.3 mg/ml) (2)	Capsule 250 mg	Corn oil

name and also shows a drug's chemical structure, water solubility, the marketed formulation, and the list of excipients.

Most solubilized oral formulations are either filled into gelatin capsules that range in size from 0.19–5.0 ml (15) or are oral solutions or elixirs that are usually intended for patients who cannot swallow a tablet or capsule, such as pediatric and elderly patients, or are used in dose-reduction regimens. Gelatin capsules dissolve in water, thus only the minimal amount of water is used in order to dissolve water-soluble excipients such as sweeteners and/or buffers. In addition, ethanol is typically minimized in soft gelatin capsule formulations because ethanol can diffuse through soft gelatin films (15).

Recently, there has been interest in polymer-based capsules, such as hydroxypropy lmethylcellulose (16,17) or polyvinylalcohol hard capsules (18,19), in order to avoid animal-derived components and to accommodate some religious and dietary considerations. Commercially available health products have used hydroxypropyl methylcellulose capsules since 1997, such as some of the products from Arkopharma in France (20). Injection-molded polyvinylalcohol hard capsules offer the advantages of controlled release, the ability to laser seal the cap and body, and close control of the size, shape, and dimensions of the capsule (19). To date, there appears to be no commercially available pharmaceutical products that use either hydroxypropyl methylcellulose or polyvinylalcohol capsules, but there are clinical trials ongoing of which details are not readily available.

Organic Solvents in Oral Formulations

Some poorly water-soluble molecules are sufficiently solubilized in solutions composed of an aqueous/organic co-solvent whereas other poorly water-soluble molecules are solubilized only in solutions that are entirely organic and composed of either one solvent or a mixture of solvents/surfactants.

Water-Soluble Organic Solvents in Oral Formulations

The water-soluble organic solvents in commercially available solubilized oral formulations are polyethylene glycol 400 (PEG 400), ethanol, propylene glycol, and glycerin, along with many water-soluble non-ionic surfactants. The most common water-soluble organic solvent for soft gelatin capsules appears to be PEG 400. Ethosuximide, a water-soluble anticonvulsant, is solubilized in PEG 400 in 250 mg Zarontin soft gelatin capsules. Bexarotene, a poorly water-soluble antineoplastic agent, is solubilized in PEG 400 in 75 mg Targretin soft gelatin capsules. Etoposide, a sparingly wa-

ter-soluble antineoplastic agent (2), is solubilized in a cosolvent mixture of PEG 400, glycerin, citric acid, and water in 50 mg VePesid soft gelatin capsules, and the oral bioavailability is 25–75% (21). The cardiotonics, nifedipine and nimodipine, are practically insoluble in water (2) and are solubilized in a cosolvent mixture of glycerin, peppermint oil, and PEG 400 in 10–30 mg Procardia and Nimotop soft gelatin capsules, respectively. Nifedipine is fully absorbed from Procardia, and the oral bioavailability is proportional to dose over 10–30 mg (21). The oral bioavailability of nimodipine from Nimotop is 13% due to first-pass metabolism (21). Digoxin is solubilized in a cosolvent mixture of propylene glycol, PEG 400, and 8% ethanol in 200-μg soft gelatin capsules. The oral bioavailability of digoxin from the solid tablets is 60–80%, but increases to 90–100% from the solubilized oral dosage form along with higher peak serum concentrations (21).

Oral solution and elixir formulations can be simple or they can be quite complex, involving many types of excipients including water-soluble organic solvents, water-insoluble organic solvents, surfactants, buffers, sugars, flavors, sweeteners, aromatics, dyes, and with/without water. Organic cosolvents are normally used to solubilize poorly water-soluble drugs to the desired concentration in oral solutions. The exact amount of solvent is usually not reported, but in those formulations where the amount is reported, the maximum amount of solvent used is up to 55% propylene glycol (the higher percentages are contraindicated in children younger than 4 years of age), up to 17% PEG 400, and up to 42% ethanol. Most over-the-counter oral solution formulations contain polyethylene glycol, propylene glycol, and/or glycerin whereas a few products contain polysorbate 20 and/or poloxamer 407 (i.e., Good Sense antihistamine liquid medication, children's Benadryl, Cepacol sore throat, and children's Sudafed).

Ritonavir, an HIV protease inhibitor with peptide-like structure, has an intrinsic water solubility of 1.0 μg/ml and two weakly basic thiazole groups with pK_as of 1.8 and 2.6 (22) (too low for pH adjustment) and is solubilized in a cosolvent mixture of propylene glycol, ethanol, water, the surfactant Cremophor EL, and peppermint oil to 80 mg/ml in the Norvir oral solution. A similar cosolvent mixture of propylene glycol, 42% ethanol, water, glycerin, the surfactant Cremophor RH 40, and peppermint oil is used to cosolubilize ritonavir to 20 mg/ml and lopinavir, a non-ionizable water-insoluble HIV protease inhibitor, to 80 mg/ml in the Kaletra oral solution.

Sirolimus is a non-ionizable and water-insoluble immunosuppressant, but is solubilized to 1 mg/ml in a solution that is entirely organic. Sirolimus is solubilized in the Rapamune oral solution using the surfactant polysorbate 80 and a proprietary solution, Phosal 50 PG, which is composed of phosphatidylcholine, propylene glycol, mono- and diglycerides, 1.5–2.5% ethanol, soy fatty acids, and ascorbyl palmitate. The oral bioavailability of sirolimus after administration of the Rapamune oral solution is approximately 14% and is increased to approximately 20% when given with a high fat diet (2). Rapamune is also available in tablets that have solid nanoparticles of sirolimus, from which the oral bioavailability is 27% higher than with the oral solution (2).

Elixirs are sweetened hydroalcoholic oral solutions that are specially formulated for oral use in infants and children. Digoxin, a non-ionizable cardiotonic glycoside, is practically insoluble in water and is solubilized in propylene glycol, 10% ethanol, flavor, sweetener, preservative, and buffers to 50 μg/ml in Lanoxin Elixir Pediatric from which the oral bioavailability is 70–85% (21). Phenobarbital, an anticonvulsant and sedative with an intrinsic water solubility of 1 mg/ml (23), is solubilized in water, 23% ethanol, glucose, sodium saccharin, and flavors to 3.5 mg/ml in Donnatal Elixir.

Water-Insoluble Organic Solvents in Oral Formulations

The water-insoluble solvents used in commercially available solubilized oral formulations include the long-chain triglycerides peanut oil, corn oil, soybean oil, sesame oil, olive oil, peppermint oil, hydrogenated vegetable oils, hydrogenated soybean oil, and the medium-chain triglycerides derived from coconut oil and palm seed. Other water-insoluble solvents include beeswax, *dl*-α-tocopherol (Vitamin E), and oleic acid. Most oily oral formulations are filled into soft gelatin capsules, but some are oral solutions.

Progesterone is a water-insoluble steroid and is solubilized in peanut oil in 100 mg Prometrium soft gelatin capsules. Dronabinol, also known as Δ-9-tetrahydrocannabinol, a natural component of cannabis used in the treatment of nausea or vomiting associated with cancer chemotherapy and also as an appetite stimulant to treat AIDS wasting syndrome, is a yellowish oil at room temperature that is solubilized by sesame oil in 2.5, 5, and 10 mg Marinol soft gelatin capsules. Dronabinol is almost completely absorbed (90–95%), but the oral bioavailability is 10–20% due to first-pass hepatic metabolism and high lipid solubility (21). Calcitrol, used in the treatment of hypocalcemia, is non-ionizable and water-insoluble, but is solubilized in a fractionated triglyceride of coconut oil in 0.25 and 0.5 μg Rocaltrol soft gelatin capsules. Calcitrol is also formulated in a fractionated triglyceride of palm seed oil in the 1 μg/ml Rocaltrol oral solution. Doxercalciferol is similar to calcitrol in chemical structure, clinical application, and formulation, and is solubilized in a fractionated medium-chain triglyceride of coconut oil and ethanol in 2.5 μg Hectorol soft gelatin capsules. Valproic acid, an anticonvulsant with an intrinsic water solubility of 1.3 mg/ml (2), is solubilized in corn oil in 250 mg Depakene soft gelatin capsules.

A mixture of water-insoluble solvents, such as beeswax and a vegetable oil, can be used to solubilize lipophilic drugs. Tretinoin, a water-insoluble antineoplastic agent, is solubilized in a combination of beeswax, soybean oil, hydrogenated vegetable oils, and hydrogenated soybean oil in 10 mg Vesanoid soft gelatin capsules. Isotretinoin, an antiacne drug, is an isomer of tretinoin and is solubilized in the same solvent mixture in 10, 20, and 40 mg Accutane soft gelatin capsules. Clofazimine, a water-insoluble antileprosy agent, is solubilized in beeswax, plant oils, and propylene glycol in 50 mg Lamprene soft gelatin capsules.

Vitamin E is the common name for *d*-α-tocopherol and is an oily liquid at room temperature and is also an antioxidant. The water-insoluble HIV protease inhibitor, saquinavir, is solubilized by a mixture of Vitamin E and medium-chain mono- and diglycerides in 200 mg Fortovase soft gelatin capsules. The oral bioavailability of saquinavir is increased by approximately 3-fold (range, 2.1- to 5.3-fold) after administering the solubilized Fortovase formulation compared to the solid dosage form Invarase (2,24). The absolute oral bioavailability of saquinavir from Fortovase formulation has not been reported, but from Invarase saquinavir's oral bioavail-

Table II. Solubilizing Excipients Used in Commercially Available Solubilized Oral and Injectable Formulations

Water-soluble	Water-insoluble	Surfactants
Dimethylacetamide (DMA)	Beeswax	Polyoxyl 35 castor oil (Cremophor EL)
Dimethyl sulfoxide (DMSO)	Oleic acid	Polyoxyl 40 hydrogenated castor oil (Cremophor RH 40)
Ethanol	Soy fatty acids	Polyoxyl 60 hydrogenated castor oil (Cremophor RH 60)
Glycerin	*d*-α-tocopherol (Vitamin E)	Polysorbate 20 (Tween 20)
N-methyl-2-pyrrolidone (NMP)	Corn oil mono-di-tridiglycerides	Polysorbate 80 (Tween 80)
PEG 300	Medium chain (C_8/C_{10}) mono- and diglycerides	*d*-α-tocopheryl polyethylene glycol 1000 succinate (TPGS)
PEG 400	Long-chain triglycerides	Solutol HS-15
Poloxamer 407	Castor oil	Sorbitan monooleate (Span 20)
Propylene glycol	Corn oil	PEG 300 caprylic/capric glycerides (Softigen 767)
Hydroxypropyl-β-cyclodextrin	Cottonseed oil	PEG 400 caprylic/capric glycerides (Labrasol)
Sulfobutylether-β-cyclodextrin (Captisol®)	Olive oil	PEG 300 oleic glycerides (Labrafil M-1944CS)
α-cyclodextrin	Peanut oil	PEG 300 linoleic glycerides (Labrafil M-2125CS)
Phospholipids	Peppermint oil	Polyoxyl 8 stearate (PEG 400 monosterate)
Hydrogenated soy phosphatidylcholine (HSPC)	Safflower oil	Polyoxyl 40 stearate (PEG 1750 monosterate)
Distearoylphosphatidylglycerol (DSPG)	Sesame oil	Peppermint oil
L-α-dimyristoylphosphatidyl-choline (DMPC)	Soybean oil	
L-α-dimyristoylphosphatidyl-glycerol (DMPG)	Hydrogenated soybean oil	
	Hydrogenated vegetable oils	
	Medium-chain triglycerides	
	Caprylic/capric triglycerides derived from coconut oil or palm see oil	

ability averaged 4% (range, 1–9%), suggesting that the oral bioavailability of saquinavir from the solubilized formulation is ~15%.

Oleic acid is the common name for (*Z*)-9-octadecenoic acid and is a nearly colorless liquid at room temperature with a melting point of 5–7°C (23). Oleic acid is practically insoluble in water, but has been used as a solvent for oral delivery of hydrophobic drugs in soft gelatin capsules (25). Oleic acid is used to solubilize ritonavir in Norvir and Kaletra soft gelatin capsules.

Surfactants (Micelles) in Oral Formulations

Water-miscible surfactant molecules contain both a hydrophobic and hydrophilic portion and can solubilize many poorly water-soluble drugs. Surfactants can also self-assemble to form micelles once the surfactant monomer concentration reaches the critical micelle concentration. Thus, surfactants can solubilize drug molecules by either a direct cosolvent effect or by uptake into micelles. The non-ionic surfactants in commercially available solubilized oral formulations include polyoxyl 35 castor oil (Cremophor EL), polyoxyl 40 hydrogenated castor oil (Cremophor RH 40), polysorbate 20 (Tween 20), polysorbate 80 (Tween 80), *d*-α-tocopherol polyethylene glycol 1000 succinate (TPGS), Solutol HS-15, sorbitan monooleate (Span 80), polyoxyl 40 stearate, and various polyglycolyzed glycerides including Labrafil M-1944CS, Labrafil M-2125CS, Labrasol, Gellucire 44/14, and Softigen 767 (Tables II and III).

Cremophor is pegylated castor oil or hydrogenated castor oil and is a complex mixture of relatively hydrophobic and hydrophilic molecules. Cremophors are synthesized by reacting either castor oil or hydrogenated castor oil with varying amounts of ethylene oxide. Polyoxyl 35 castor oil is also known as Cremophor EL (BASF, Inc., Ludwigshafen, Germany) or Etocas 35 (Croda, Inc., Parsippany, NJ, USA) and is a mixture of 83% relatively hydrophobic and 17% relatively hydrophilic components. The major component of polyoxyl 35 castor oil's relatively hydrophobic portion is glycerol polyethylene glycol ricinoleate, and the major components of the relatively hydrophilic portion are polyethylene glycols and glycerol ethoxylates (Table III). The critical micelle concentration of polyoxyl 35 castor oil is ~0.009% (0.090 mg/ml). Polyoxyl 35 castor oil is a pale yellow viscous liquid, which is clear at temperatures above 26°C (26). Polyoxyl 40 hydrogenated castor oil is also known as Cremophor RH 40 (BASF, Inc.) and is a mixture of approximately 75% relatively hydrophobic of which a major portion is glycerol polyethylene glycol 12-oxystearate (Table III).

Cremophors are quite effective at solubilizing very hydrophobic drugs and are normally not used alone. Cremophor RH 40 is one of the components of the lopinavir and ritonavir Kaletra oral solution, and the cyclosporin Neoral microemulsion oral solution and soft gelatin capsule. Cremophor EL is one of the components of the cyclosporin Gengraf microemulsion, the ritonavir Norvir oral solution and soft gelatin capsule, and the ritonavir and lopinavir Kaletra soft gelatin capsules.

There are many different polyglycolyzed glycerides, and they are generally used to formulate water-insoluble drugs in lipid-based formulations such as self-emulsifying drug delivery systems (SEDDS) in order to improve oral bioavailability (27,28). The non-ionic polyglycolyzed glycerides in solubilized oral formulations include polyoxyethylated oleic glycerides (Labrafil M-1944CS), polyoxyethylated linoleic glycerides (Labrafil M-2125CS), and polyoxyethylated caprylic/capric glycerides (Labrasol), and the main molecular components are shown in Table III. Labrafil M-1944CS is obtained by the partial pegylation of apricot kernel oil and consists of mono-, di-, and triglycerides and mono- and difatty acid esters of PEG 300, with the main fatty acid being oleic acid. Labrafil M-2125CS is obtained by the partial pe-

Table III. Chemical Structures of Selected Solubilizing Excipients

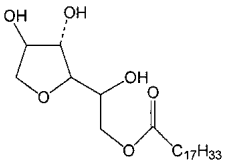
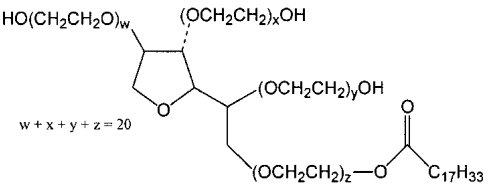
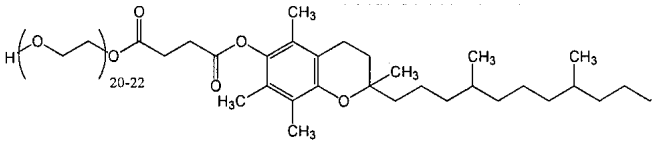
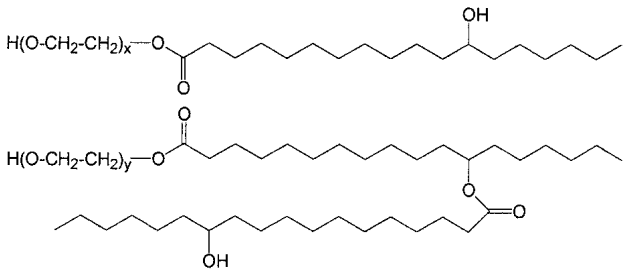
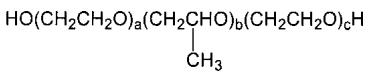
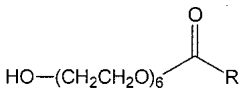
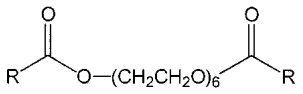
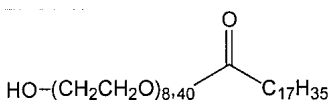
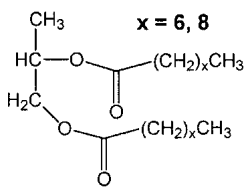
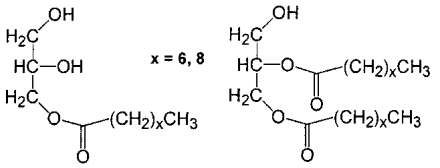
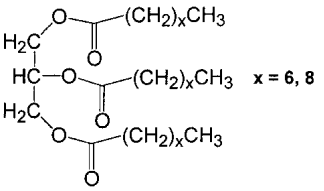
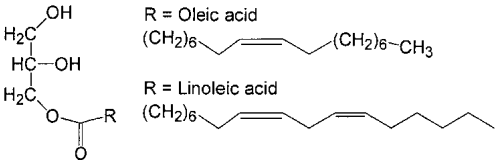
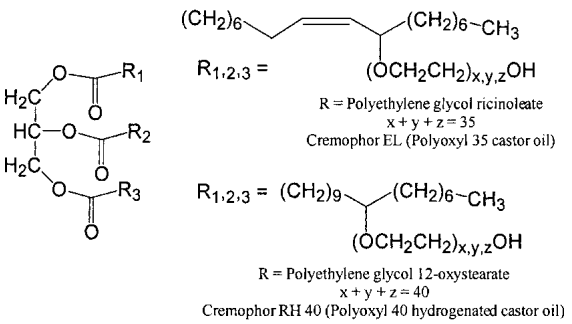
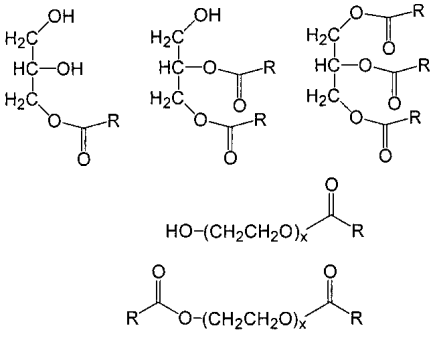
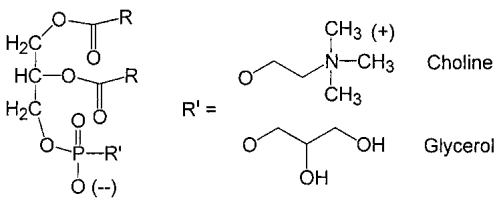
Excipient name and/or common name(s)	Chemical structure
Sorbitan monooleate, Span 80 MW = 428	
Polyoxyethylene 20 sorbitan monooleate, Polysorbate 80, Tween 80 MW = 1310	
d-α tocopheryl polyethylene glycol 1000 succinate, Vitamin E TPGS MW ~ 1513	
Solutol HS 15 (polyethyleneglycol 660 12-hydroxystearate)*	
Poly(ethyleneoxide)/ poly-(propyleneoxide/ poly(ethyleneoxide) triblock copolymers (Poloxamers, Pluronics) Poloxamer 407 (Pluronic F-127) has 200 residues of ethylene oxide and 65 residues of propylene oxide and a molecular weight of 12,500 Da	
Mono- and di-fatty acid esters of PEG 300 Example: Polyoxyl oleate (polyethylene glycol monooleate)	 R = C_7–C_{17}, oleate  R = C_7–C_{17}, oleate
Mono-stearic acid ester of PEG 400 or 1750 (Polyoxyl 40 stearate is in the over the counter Vicks 44 line of oral solutions)	 Polyoxyl 8 stearate (PEG 400 monostearate) Polyoxyl 40 stearate (PEG 1750 monostearate)
Propylene glycol dicaprylate/dicaprate Miglyol 840	

Table III. Continued

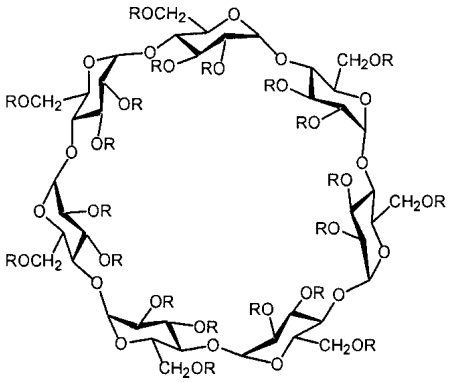
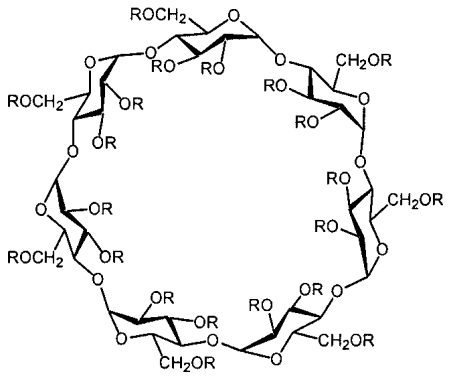
Excipient name and/or common name(s)	Chemical structure
Medium chain mono- and diglycerides Capmul Imwitor 742	
Medium-chain triglycerides (Caprylic and capric triglycerides) Labrafac Miglyol 810, 812 Crodamol GTCC-PN Softison 378 (x = 10)	
Long-chain monoglycerides Glyceryl monooleate (Peceol) Glyceryl monolinoleate (Maisine)	
Polyoxyethylene castor oil derivatives, Cremophor EL and Cremophor RH 40†	Relatively hydrophobic molecules
Complex mixture of 75–83% relatively hydrophobic molecules, and 17–25% relatively hydrophilic molecules (polyethylene glycol and glycerol ethoxylates)	
Mono-, di-, and triglycerides and mono- and di-fatty acid esters of PEG (also contains glycerol and PEG)	
Phospholipids	

Example	x	R
Softigen 767	6	C_8, C_{10}
Labrasol‡	8	C_8, C_{10}
Labrafil M-1944CS§	6	$C_{18:1}$
Labrafil M-2125CS¶	6	$C_{18:2}$
Gelucire 44/14‖	32	$C_{C12}C_{14}$

Example	R	R′
DSPG	C_{18}	Glycerol
DMPC	C_{14}	Choline
DMPG	C_{14}	Glycerol

gylation of corn oil and consists of mono-, di-, and triglycerides and mono- and di-fatty acid esters of PEG 300, with the main fatty acid being linoleic acid. Labrafil M-1944CS and Labrafil M-2125CS are liquids at 40–45°C. Gelucire 44/14 (melting point 44°C and HLB value of 14) is obtained by the polyglycolysis of hydrogenated palm kernel oil and PEG 1500 and is used to solubilize 200 mg of the water-insoluble cholesterol-lowering agent fenofibrate in Cil (Germany) and Lipirex (France). Labrasol is obtained by the polyglycolysis of medium-chain triglycerides from coconut oil and PEG 400

Table III. Continued

Excipient name and/or common name(s)	Chemical structure
Hydroxypropyl-β-cyclodextrin, ** average degree of substitution: 4 (Encapsin) 8 (Molecusol)	 OH R = H or CH_2CHCH_3
Sulfobutylether-β-cyclodextrin, †† average degree of substitution: 6.5 MW = 2163, Captisol	 R = H or $CH_2CH_2CH_2CH_2SO_3Na$

* Solutol HS 15 is ~70% lipophilic consisting of polyglycol mono- and diesters of 12-hydroxystearic acid and ~30% hydrophilic consisting of polyethylene glycol. Solutol HS 15 is synthesized by reacting 12-hydroxystearic acid with 15 moles of ethylene oxide.

† Cremophors are complex mixtures of various hydrophobic and hydrophilic components. Cremophor EL is obtained by reacting 35 moles of ethyleneoxide with 1 mole of castor oil and comprises about 83% hydrophobic constituents of which the main component is glycerol polyethylene glycol ricinoleate. Cremophor RH 40 is obtained by reacting 40 moles of ethyleneoxide with 1 mole of hydrogenated castor oil and comprises about 75% hydrophobic constituents of which the main component is glycerol polyethylene glycol 12-hydroxystearare.

‡ Labrasol is a mixture of mono-, di-, and triglycerides and mono- and di-fatty acid esters of PEG 400. Labrasol is synthesized by an alcoholysis/esterification reaction using medium-chain triglycerides from coconut oil and PEG 400, and the main fatty acid is caprylic/capric acids.

§ Labrafil M-1944 CS is a mixture of mono-, di-, and triglycerides and mono- and di-fatty acid esters of PEG 300. Labrafil M-1944 CS is synthesized by an alcoholysis/esterification reaction using apricot kernel oil and PEG 300, and the main fatty acid is oleic acid (58–80%).

¶ Labrafil M-2125 CS is a mixture of mono-, di-, and triglycerides and mono- and di-fatty acid esters of PEG 300. Labrafil M-2125 CS is synthesized by an alcoholysis/esterification reaction using corn oil and PEG 300, and the main fatty acid is linoleic acid (50–65%).

‖ Gelucire 44/14 is a mixture of mono-, di-, and triglycerides and mono- and di-fatty acid esters of PEG 1500. Gelucire 44/14 is synthesized by an alcoholysis/esterification reaction using palm kernel oil and PEG 1500, and the main fatty acid is lauric acid.

†† It is unclear as to which of the three hydroxyls (primary 6′ or the secondary 2′ or 3′) substitution occurs.

and is used to formulate 20 mg of the sparingly water-soluble NSAID piroxicam in Piroflam-Li (Germany) (27).

The hard gelatin capsule formulation of ritonavir was initially marketed as an amorphous semi-solid dispersion consisting of caprylic/capric medium-chain triglycerides, polyoxyl 35 castor oil, citric acid, ethanol, polyglycolyzed glycerides, polysorbate 80, propylene glycol, and 100 mg of ritonavir as Norvir (29). However, due to crystallization of amorphous ritonavir to an insoluble crystal form (i.e., a new polymorph) as the drug product sat on the shelf, the dissolution and hence the oral bioavailability were adversely affected and the product was temporarily withdrawn from the market in 1998 (30,31). Norvir was reintroduced in 1999 after switching to a thermodynamically stable solution formulation containing 100 mg of ritonavir dissolved in a mixture of oleic acid, Cremophor EL, ethanol, and the antioxidant BHT and filled into soft gelatin capsules. However, Norvir is being replaced by Kaletra oral solution and soft gelatin capsule which is a combination of 133.3 mg of lopinavir and 33.3 mg of ritonavir dissolved in a mixture of oleic acid, polyoxyl 35 castor oil (Cremophor EL), and propylene glycol.

The micelle-forming molecule *d*-α-tocopherol polyethyl-

ene glycol 1000 succinate (TPGS) (Table III) was first discovered in 1950 at Eastman Kodak Company (32) and "it has been recognized as an effective oral absorption enhancer for improving the bioavailability of poorly absorbed drugs and as a vehicle for lipid-based drug delivery" (33). TPGS is also a water-soluble source of the water-insoluble oil Vitamin E. The HIV protease inhibitor, amprenavir, is poorly water-soluble and is solubilized in a combination of ~23% TPGS, ~60% PEG 400, and ~5% propylene glycol in 50 or 150 mg Agenerase soft gelatin capsules. Amprenavir is solubilized in a combination of ~12% TPGS, ~17% PEG 400, and ~55% propylene glycol to 15 mg/ml in Agenerase oral solution. However, Agenerase oral solution is contraindicated in infants and children below the age of 4 years because of the potential risk of toxicity from the large amount of propylene glycol (~1650 mg/kg per day). The absolute oral bioavailability of amprenavir has not been established, but the oral solution was 13% less bioavailable compared to soft gelatin capsules (21). The oral bioavailability of amprenavir in conventional capsule or tablet formulations is near zero, but in TPGS-containing formulations the oral bioavailability in beagle dogs at 25 mg/kg increases to 69 ± 8% with 20% TPGS and 80 ± 16% with 50% TPGS (32). TPGS forms micelles at concentrations ≥0.2 mg/ml in water and improves the aqueous solubility of amprenavir from 36 μg/ml to 720 μg/ml (34). It was also shown, by directional transport through Caco-2 cell monolayers, that TPGS is a potent inhibitor of an active efflux even at concentrations 10-fold below the critical micelle concentration (34), suggesting that monomeric TPGS is capable of inhibiting the efflux mechanism. Therefore, TPGS not only improves *in vivo* performance by solubility-enhancing micelle formation, but also by increasing the overall intestinal permeability via inhibiting an efflux mechanism.

Sorbitan monooleate, also known as Span 80, is a yellow viscous liquid at room temperature (26) and is the ester of oleic acid and the cyclic hexitol of sorbitol (Table III). Polysorbates are surfactants that are pegylated derivatives of sorbitan monoesters (i.e., monolaurate, monopalmitate, monostearate, monooleate, or monoisostearate) or sorbitan triesters (i.e., tristearate or trioleate) and are available in many grades (26). Polysorbate 80, also known as Tween 80, is a mixture of polyoxyethylene 20 sorbitan monooleates, as shown in Table III, and is a yellow viscous liquid at room temperature. Sorbitan monooleate, polysorbate 80, and unsaturated polyglycolyzed glycerides (Labrafils) are components in the cyclosporin formulations Gengraf and Sandimmune.

Mono- and diglycerides of caprylic/capric acid are used to solubilize 0.5 mg of dutasteride in Avodart soft gelatin capsules for the treatment of benign hyperplasia. The oral bioavailability of durasteride is 40–94% with an average of 60% (Ref. 3; see www.rxlist.com for the product insert).

Microemulsion Oral Formulations

Microemulsions are thermodynamically stable isotropically clear dispersions composed of a polar solvent, an oil, a surfactant, and a cosurfactant. Microemulsions have much potential for drug delivery because very hydrophobic molecules can be solubilized and formulated for oral administration (35). The few commercial products are actually nonaqueous microemulsions, also known as microemulsion preconcentrates, as the polar solvent is ethanol and not water. Upon contact with aqueous media, such as gastrointestinal fluids, a nonaqueous microemulsion spontaneously forms a fine dispersion or aqueous microemulsion.

Cyclosporin A is a sparingly water-soluble lipophilic cyclic peptide with a molecular weight of 1201 Da used in preventing rejection of transplanted kidneys, livers, and hearts and is commercially available in multiple solubilized oral formulations. Cyclosporin A was originally formulated as Sandimmune in 25, 50, and 100 mg soft gelatin capsules as well as a 100 mg/ml oral solution. The Sandimmune soft gelatin capsules contain cyclosporin A dissolved in 12.7% ethanol, corn oil, glycerol, and Labrafil M-2125CS whereas the oral solution contains 12.5% ethanol, olive oil, and Labrafil M-1944CS. The absolute oral bioavailability of cyclosporin A as Sandimmune is erratic and is <10% in liver transplant patients and as high as 89% in some renal transplant patients (2). To improve the oral bioavailability, cyclosporin A was reformulated as a microemulsion and solubilized in 11.9% ethanol, corn oil-mono-di-triglycerides, polyoxyl 40 hydrogenated castor oil (Cremophor RH 40), and propylene glycol in 25 or 100 mg Neoral soft gelatin capsules as well as a 100 mg/ml oral solution. After oral administration of Neoral, the cyclosporin A area under the curve of the plasma concentration vs. time profile is 20–50% higher than with Sandimmune (2). Also, the peak plasma concentrations of cyclosporin A are 40–106% higher after oral administration of Neoral compared to Sandimmune. The Gengraf cyclosporin A formulation is a hard gelatin capsule (no oral solution) containing 25 or 50 mg of cyclosporin A dissolved in 12.8% ethanol, polyethylene glycol, polyoxyl 35 castor oil (cremophor EL), polysorbate 80, propylene glycol, and sorbitan monooleate and "forms an aqueous dispersion in an aqueous environment" (2). Gengraf and Neoral are bioequivalent with virtually identical pharmacokinetics. Another cyclosporin A soft gelatin capsule contains Labrasol (Table III) as the solubilizing excipient and is a product of Sidmak Laboratories.

Acids (pH Adjustment) in Oral Formulations

A drug with a basic functional group may be solubilized in acidic solutions at pH values below the drug's pK_a. The pH of acidic oral aqueous solution is usually controlled by the salt form used or by hydrochloric acid, tartaric acid, benzoic acid, or citric acid. For example, risperidone is a tertiary amine antipsychotic that is practically insoluble at neutral pH and is solubilized in water, tartaric acid, and benzoic acid to 1 mg/ml in the Resperdal oral solution (2). Loratadine is widely used in the treatment of allergies and is a pyridine analog that is not soluble in neutral pH water, but is solubilized by citric acid at pH 2.5–3.1 and a cosolvent mixture of water, glycerin, and propylene glycol to 1 mg/ml in Claritin syrup.

Cyclodextrin Complexation in Oral Formulations

Cyclodextrins are cyclic (α-1,4)-linked oligosaccharides of α-D-glucopyranose containing a relatively hydrophobic central cavity and a hydrophilic outer surface (36). Cyclodextrins are designated α, β, or γ corresponding to 6, 7, or 8 glucopyranose units, with cavity diameters of 4.7–5.3, 6.0–6.5, and 7.5–8.3 Å, respectively (37). The central cavity is lined with methylene groups ($-CH_2-$) and ethereal oxygens of the glucopyranose units, and is estimated to have a polarity simi-

lar to that of aqueous ethanolic solutions (36). Cyclodextrins can increase the equilibrium solubility of some hydrophobic molecules by forming a noncovalent inclusion complex if the molecule, or a portion of the molecule (i.e., nonpolar sidechain or an aromatic or heterocyclic ring) is of the appropriate size to fit inside the central cavity.

In recent years, there has been a tremendous amount of research and development devoted to cyclodextrin-based drug delivery (13,36–40) which has resulted in several commercial oral and injectable cyclodextrin-based products throughout the world. Therefore, it is now very clear that certain cyclodextrin excipients, when matched with their appropriate routes of delivery, are safe, effective, and "acceptable" for human *in vivo* use. There are at least 21 commercial cyclodextrin-based pharmaceutical products of which 11 are marketed in Europe, 9 in Japan, and 6 in the United States with more cyclodextrin-based products awaiting regulatory approval (38). Most of the commercial cyclodextrin-based products are for oral administration as tablets, capsules, oral solutions, or a gargling solution. There are also two suppositories, one eye drop, and one ointment along with various injectable products. All of the solid cyclodextrin-based formulations use either α- or β-cyclodextrin. The β-form is the most commonly used, but its solubility in water is limited to ~18 mg/ml. However, covalent modifications can dramatically improve the water solubility and safety of cyclodextrins (39). The two most common and preferred water-soluble β-cyclodextrin derivatives are hydroxypropyl-β-cyclodextrin and sulfobutylether-β-cyclodextrin, which have an average degree of substitution of 4–8 surface modifications per β-cyclodextrin molecule (Table III). Itraconazole, a weakly basic (pK_a ~3.7) water-insoluble antifungal drug, is solubilized to 10 mg/ml using a combination of 40% hydroxypropyl-β-cyclodextrin (i.e., ~400 mg/ml) in water and pH adjustment to ~2 in Sporanox oral solution. The relative oral bioavailability of itraconazole from the oral solution is 149% ± 68% compared to capsules (21) from which the oral bioavailability is 55% (21). Therefore, the oral bioavailability of itraconazole from the oral solution can be estimated to be 45–82%.

INJECTABLE FORMULATIONS

The solubilization techniques for injectable formulations are similar to those in oral formulations and include pH adjustment, mixed aqueous/organic cosolvents, organic solvent mixtures, cyclodextrin complexation, emulsion, liposomes, polymeric gels, and combinations of techniques (5,6,8,41). This section focuses on solution injectable formulations for intravenous bolus, intravenous infusion, intramuscular, subcutaneous, and local administration. Tables IV and V are selected listings of aqueous and nonaqueous, commercially available injectable solution formulations.

Buffers, pH Adjustment in Injectable Formulations

A drug molecule that is ionizable can often be solubilized to the desired concentration by pH adjustment if the drug's pK_a is sufficiently away from the formulation pH value. The acceptable range is pH 2–12 for intravenous and intramuscular administration, but subcutaneously the range is reduced to pH 2.7–9.0 as the rate of *in vivo* dilution is significantly reduced resulting in more potential for irritation at the injection site. The solution pH is controlled by either the salt form of the drug, strong acids/bases such as hydrochloric acid or sodium hydroxide, or a buffer such as glycine, citrate, acetate, histidine, phosphate, tris(hydroxymethyl)aminomethane (TRIS), or carbonate in which case the buffer concentration must be high enough to maintain the desired pH (5–8) but must be balanced by *in vivo* tolerability considerations (42).

Mixed Organic/Aqueous Injectable Formulations

The combination of an aqueous solution and a water-soluble organic solvent/surfactant (i.e., a cosolvent) is often used in injectable formulations when pH adjustment alone is insufficient in achieving the desired solution concentration (12,43). The water-soluble organic solvents and surfactants used in commercially available injectable formulations are listed in Table VI and include propylene glycol, ethanol, polyethylene glycol 300, polyethylene glycol 400, glycerin, dimethylacetamide (DMA), *N*-methyl-2-pyrrolidone (NMP; Pharmasolve), dimethylsulfoxide (DMSO), Solutol HS 15, Cremophor EL, Cremophor RH 60, and polysorbate 80. Many cosolvent formulations are marketed using rather high concentrations of organic solvent and are usually but not always diluted prior to injection.

Limitations in using organic solvents in injectable products include possible precipitation, pain (44), inflammation, and hemolysis upon injection. The *in vivo* compatibility of organic solvents administered by intravenous (45–50), intramuscular (51–53), and subcutaneous (54) injection has been studied by various researchers. Intravenous compatibility can be predicted *in vitro* by measuring the percentage solvent concentration that induces hemolysis in 50% of healthy red blood cells, LD_{50}. A higher LD_{50} implies a more compatible solvent. Using this hemolysis method, the following LD_{50}s were measured: 37% DMA, 30% PEG 400, 21% ethanol, 10% (ethanol/propylene glycol, 10/40), 5.7% propylene glycol, and 5.1% DMSO (45). These findings are consistent with other research (49) that showed propylene glycol produced a large hemolytic response both *in vivo* and *in vitro*, but the hemolysis could be reduced by either a tonicifying agent or PEG 400. Therefore, although propylene glycol is the most common organic solvent in injectable formulations, it is clearly not as biocompatible as PEG 400, ethanol, or DMA.

For intravenous bolus injection, the amount of organic solvent administered is up to 68% propylene glycol (phenobarbitol), 50% PEG 300 (methocarbamil), 20% ethanol (paricalcitrol), 15% glycerin (dihydroergotamine), and 9% PEG 400 (lorazepam). For intravenous infusion, the amount of organic solvent administered is up to 25% polysorbate 80 (docetaxel), 15% glycerin (dihydroergotamine), 10% Cremophor EL (paclitaxel), 13% ethanol (docetaxel), and 6% propylene glycol (melphalan). The intramuscular route has similar *in vivo* constraints to the intravenous route, but can tolerate as much as 100% organic solvent and is usually limited to less than 5 ml per injection site. The subcutaneous route has the most constraints when using cosolvent due to the reduced volume flow away from the injection site compared to intravenous and intramuscular. As a result, only a few cosolvent products are administered subcutaneously, and the amount of organic solvent is limited to 6% ethanol and 15% glycerin (dihydroergotamine) or 7% polyoxyethylated fatty acid (phtyonadione, vitamin K_1), and the volume is typically 1–2 ml. However, 0.25–0.50 ml of a solution containing 55–66%

Table IV. List of Selected Commercially Available Aqueous-Based Solubilized Injectable Formulations

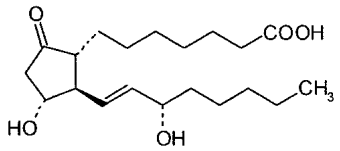
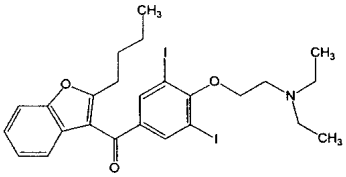
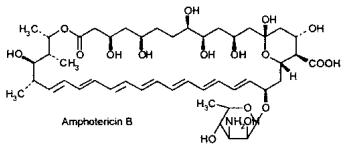
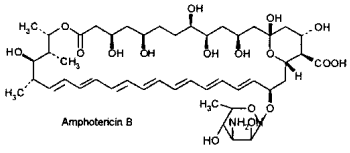
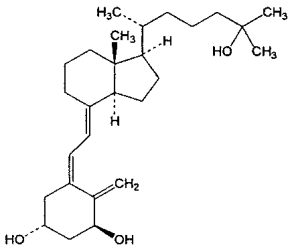
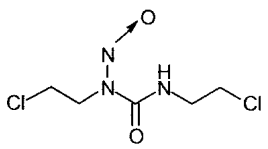
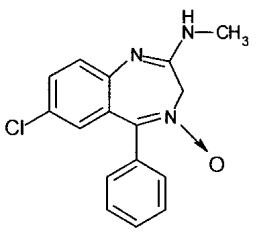
Molecule/ Trade Name/ Company/ Indication	Chemical structure	Formulation	Preparation	Administration	Solubilization technique
Alprostadil (PGE_1)/ Edex/ Schwarz/ Erectile dysfunction		Lyophilized powder 12–50 μg α-cyclodextrin 400–1610 μg Lactose 56 mg pH 4–8	Reconstitute with 1.2 ml saline	Intracavernous	Cyclodextrin complexation 12:1 mole ratio CD:drug
Amiodarone HCl/ Cordarone/ Wyeth-Ayerst/ Antiarrhythmic, antianginal		Solution 50 mg/ml, Polysorbate 80 at 10%, Benzyl alcohol 2% pH 4.1	Dilute with D5W to <2 mg/ml	IV infusion	Weak base pH < pK_a, and cosolvent, micelles
Amphotericin B/ Ambisome/ Gilead/ Antifungal		Lyophilized powder 50 mg HSPC 18 mg/ml, DSPG 7 mg/ml, Cholesterol 4 mg/ml, α-tocopherol 0.05 mg/ml, Sucrose 75 mg/ml, Disodium succinate 2 mg/ml pH 5.0–6.0	Reconstitute with WFI to a 4 mg/ml Dilute to 1–2 mg/ml with D5W	IV infusion	Liposome
Amphotericin B/ Abelcet/ Elan/ Antifungal		Solution 5 mg/ml DMPC 3.4 mg/ml, DMPG 1.5 mg/ml, Sodium chloride 9 mg/ml pH = 5–7	Dilute to 1–2 mg/ml with D5W	IV infusion	Lipid complex
Calcitriol/ Calcijex/ Abbott/ Management of hypocalcemia in patientsundergoing chronic renal dialysis		Solution 1–2 μg/ml, Polysorbate 20 at 4 mg/ml, Sodium ascorbate 10 mg/ml, Sodium chloride 1.5 mg/ml, EDTA 1.1 mg/ml, Sodium phosphates 9.2 mg/ml, pH 6.5–8.0	None	IV bolus	Micelles
Carmustine/ BiCNU/ Bristol-Myers-Squibb/ Antineoplastic		Lyophilized solid 100 mg pH 5–6	Reconstitute with 3 ml of ethanol, then further dilute with 27 ml WFI	IV infusion	Ethanol
Chlordiazepoxide HCl/ Librium/ ICN/ Tranquilizer	 pKa = 4.8	Powder 100 mg supplied diluent: Propylene glycol 20% Tween 80 at 4%, Benzyl alcohol 1.5%, Maleic acid 1.6% pH = 3	Reconstitute with supplied diluent to 50 mg/ml for IM. Reconstitute with saline or WFI to 20 mg/ml for IV bolus	IM/Slow IV bolus over 1 min	Weak base pH < pK_a, and cosolvent

Table IV. Continued

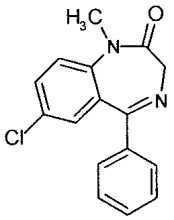
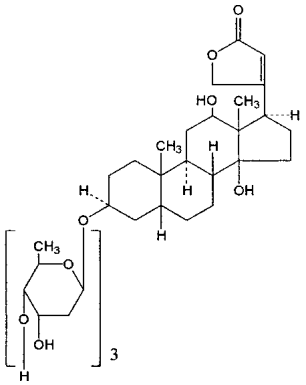
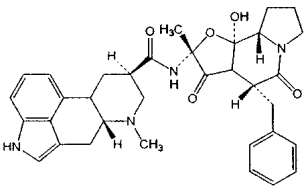
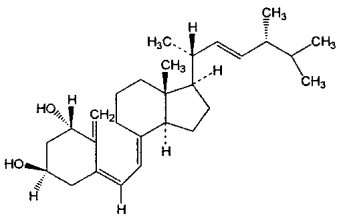
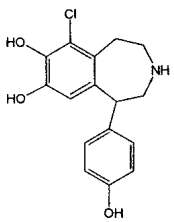
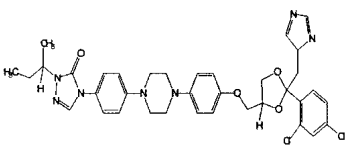
Molecule/ Trade Name/ Company/ Indication	Chemical structure	Formulation	Preparation	Administration	Solubilization technique
Diazepam/ Valium/ Roche/ Management of anxiety disorders, skeletal muscle relaxant	 pKa = 3.3	Solution 5 mg/ml Propylene glycol 40%, Ethyl alcohol 10%, Benzyl alcohol 1.5%, Sodium benzoate 5%, Benzoic acid pH 6–7	None	IM/IV IV through running IV tube	Cosolvent
Digoxin/ Lanoxin/ Glaxo SmithKline/ Cardiotonic		Solution 0.25 mg/ml Propylene glycol 40%, Ethyl alcohol 10%, Sodium phosphate, 0.17% Citric acid 0.08% pH of 6.8 to 7.2	None or can be diluted 4-fold with WFI, slaine or D5W, but must be used immediately due to precipitation	IV over 1–5 minutes/ rarely IM due to pain with IM ingection	Cosolvent
Dihydroergotamine mesylate/ D.H.E 45/ Novartis/ Migraine headaches		Solution 1 mg/ml Glycerin 15%, Ethyl alcohol 6.1%, pH 3.6	None	IV bolus/ IM/ SC	Weak base pH < pK_a, and cosolvent
Doxercalciferol/ Hectorol/ Bone care, management of secondary hyper-parathyroidism associated with chronic renal dialysis		Solution 2 μg/ml Polysorbate 80 at 4 mg/ml, Sodium chloride 1.5 mg/ml, Sodium ascorbate 10 mg/ml, Sodium phosphates dibasic 9.4 mg/ml, Disodium EDTA 1.1 mg/ml	None	IV bolus	Micelles
Fenoldopam mesylate/ Corlopam/ Abbott/ Antihypertensive	 pK_a = 4.5	Solution 10 mg/ml Propylene glycol 50%, Sodium metabisulfite 1 mg/ml, Citric acid 3.4 mg/ml, Sodium citrate 0.61 mg/ml pH ~ 3	Dilute with saline or D5W to 0.04 mg/ml	IV infusion	Weak base pH < pK_a and cosolvent
Itraconazole/ Sporanox/ Ortho Biotech and Janssen/ Antifungal	 pK_a = 3.7	Solution 10 mg/ml Hydroxypropyl-β-cyclodextrin 40%, Propylene glycol 2.5%, pH 4.5	Dilute with saline to 5 mg/ml	IV infusion	Cyclodextrin complexation

Table IV. Continued

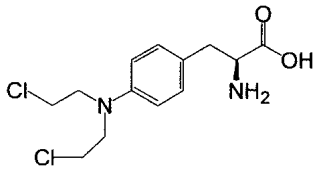
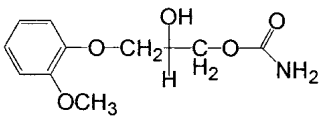
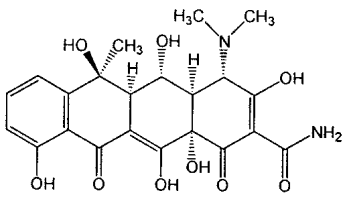
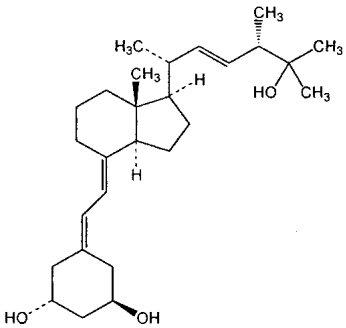
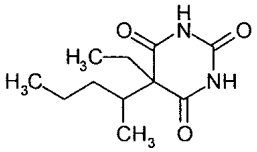
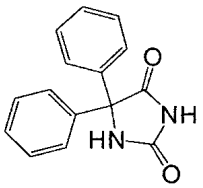
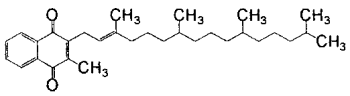
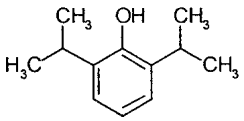
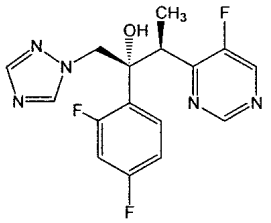
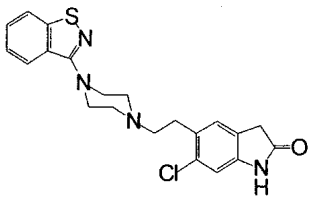
Molecule/ Trade Name/ Company/ Indication	Chemical structure	Formulation	Preparation	Administration	Solubilization technique
Melphalan HCl/ Alkeran/ Glaxo SmithKline/ Antineoplastic, alkylating agent		Lyophilized powder 50 mg Povidone 20 mg. Provided 10 ml diluent: Water 35%, Propylene glycol 60%, Ethyl alcohol 5%, Sodium citrate 0.2 g pH 6.5–7.0	Reconstitute vigorously with provided diluent to 5.0 mg/ml, then further dilute with saline to 0.45 mg/ml	IV infusion over 15–20 minutes	Cosolvent
Methocarbamil/ Robaxin/ A.H. Robbins/ Skeletal muscle relaxant		Solution 100 mg/ml, PEG 300 50%, pH = 4–5	None for IM or IV bolus. For IV infusion dilute with = 250 ml saline or D5W	IM/IV bolus/ IV infusion	Cosolvent
Oxytetracycline/ Terramycin/ Pfizer/ Antibiotic		Solution 50–125 mg/ml, Lidocaine 20 mg/ml, Propylene glycol 67–75%, Monothioglycerol 10 mg/ml, Magnesium chloride 25–60 mg/ml, Ethanolamine 17–42 mg/ml, Citric acid 10 mg/ml, Propyl gallate 0.2 mg/ml pH ~ 3	None	IM	Weak base pH < pK_a and cosolvent
Paricalcitol/ Zemplar/ Abbott/ Treatment of secondary hyperparathyroidism associated with chronic failure		Solution 0.005 mg/ml Propylene glycol 30%, Ethyl alcohol 20%	None	IV bolus	Cosolvent
Pentobarbital sodium/ Nembutal/ Abbott/ Anticonvulsant, sedative, hypnotic, anesthetic	 $pK_a = 8.0$	Solution 50 mg/ml, Propylene glycol 40%, Ethyl alcohol 10% pH 9.5	None or dilute with saline, D5W or lactated Ringer's	IM/slow IV bolus	Weak acid pH > pK_a and cosolvent

Table IV. Continued

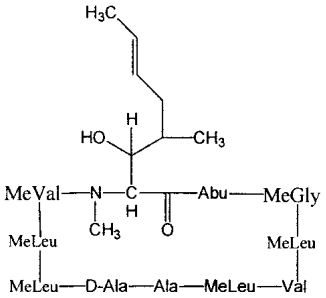
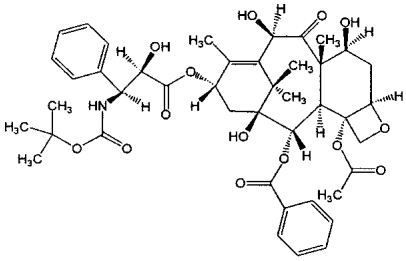
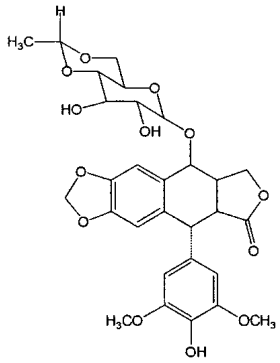
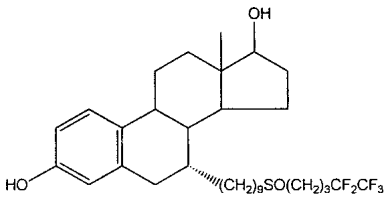
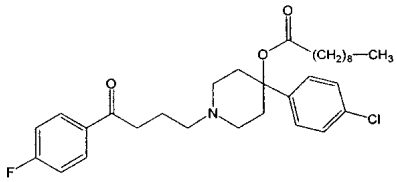
Molecule/ Trade Name/ Company/ Indication	Chemical structure	Formulation	Preparation	Administration	Solubilization technique
Phenytoin sodium/ Dilantin/ Elkins-Sinn/ Anticonvulsant	 $pK_a = 8.3$	Solution 50 mg/ml Propylene glycol 40%, Ethyl alcohol 10% pH 10–12.3	None	IM/IV bolus	Weak acid pH > pK_a and cosolvent
Phytonadione (Vitamin K_1) Aqua-MEPHYTON/ Merck/ Vitamin K deficiency		Aqueous dispersion 2–10 mg/ml Polyoxyethylated fatty acid 70 mg/ml, Dextrose 37 mg/ml, Benzyl alcohol 0.9%, pH 3.5–7	None for SC, IM or IV bolus. For IV infusion dilute with saline, D5W or lactated Ringer's	SC/IM/IV bolus/ IV infusion	Aqueous dispersion
Propofol/ Diprivan 1%/ AstraZeneca/ Anesthetic, sedative	 $pK_a = 11$	Emulsion, 10 mg/ml Soybean oil 100 mg/ml, Glycerol 22.5 mg/ml, Egg lecithin 12 mg/ml, EDTA	None (shake well)	IV bolus/IV infusion	Emulsion
Voriconazole/ Vfend/ Pfizer/ Antifungal		Lyophilized powder 200 mg Sulfobutylether-ß-cyclodextrin 3200 mg	Reconstitute with water to 10 mg/ml. Dilute with saline, D5W or lactated Ringers to ⩽ 5 mg/ml	IV infusion	Cyclodextrin complexation
Ziprasidone mesylate/ Geodon/ Pfizer/ Antipsychotic		Lyophilized powder 24 mg Sulfobutylether-ß-cyclodextrin 350 mg	Reconstitute. with 1.2 ml water to 20 mg/ml.	IM	Cyclodextrin complexation

N-methyl-2-pyrrolidone (leuprolide acetate in Eligard) is injected subcutaneously in which there is a transient slight warm or burning sensation, but of no real concern (55,56).

Propylene glycol is the most common organic solvent in commercially available injectable formulations. Fenoldopam mesylate, a sparingly water-soluble rapid-acting vasodilator antihypertensive, is solubilized in Corlopam to 10 mg/ml in a citric acid pH 3.4 buffer with 50% propylene glycol which is diluted at least 50-fold with saline or dextrose 5% prior to IV infusion (2). Oxytertacycline, a tertiary amine antibiotic, has solubility at pH 2 of ~4.6 mg/ml (23) and is solubilized in Terramycin to 50–125 mg/ml with 67–75% propylene glycol and 1% citric acid and injected undiluted intramuscularly. Chlordiazepoxide, a tranquilizer, is formulated in Librium as a lyophilized powder that is reconstituted to 50 mg/ml with a supplied diluent consisting of water, 20% propylene glycol, and 4% polysorbate 80 and is injected undiluted intramuscularly.

Ethanol is a common solubilizing excipient and is often used in conjunction with propylene glycol in mixed aqueous/ organic cosolvents or with Cremophor EL in formulation composed entirely of organic solvents. Ketorolac trometh-

Table V. List of Selected Commercially Available Nonaqueous Solubilized Injectable Formulations

Molecule/ Trade Name/ Company/ Indication	Chemical structure	Formulation	Preparation	Administration
Cyclosporin/ Sandimmune/ Novartis/ Immunosuppressant		50 mg/ml Cremophor EL 65%, Ethyl alcohol 35%, blanketed with nitrogen	Dilute with saline or D5W to 0.5–2.5 mg/ml	IV infusion over 2–6 h
Docetaxel/ Taxotere/ Rhone-Poulenc Rorer/ Antineoplastic		40 mg/ml Polysorbate 80	Dilute with provided diluent of water with 13% ethanol to 10 mg/ml, then further dilute to 0.3–0.74 mg/mL with saline or D5W.	IV infusion over 1 h
Etoposide/ VePesid/ Bristol-Myers-Squibb/ Antineoplastic		20 mg/ml PEG 300 at 60%, Ethyl alcohol 30%, Tween 80 at 8.0%, Benzyl alcohol 3.0%, Citric acid 2 mg/ml pH = 3–4	Dilute with saline or D5W to 0.2–0.4 mg/ml	IV infusion over 30–60 min
Fulvestrant/ Faslodex®/ AstraZeneca/ Antineoplastic		50 mg/ml Ethyl alcohol Benzyl alcohol Benzyl benzoate Castor Oil	None	IM
Haloperidol Decanoate/ Haldol Decanoate/ Ortho-McNeil/ Antipsychotic	 $pK_a = 8.3$	50–100 mg/ml Sesame Oil Benzyl alcohol 1.2%	None	IM

amine, a carboxylic acid nonsteroidal anti-inflammatory, is formulated in Toradol at 15–30 mg/ml with 10% ethanol in a pH 7–8 citric acid buffer that is administered undiluted by intramuscular or intravenous injection. Ethanol is used for both solubility and stability reasons in the injectable formulation of carmustine, BiCNU. Carmustine is an antineoplastic agent that has maximum water solubility of 4 mg/ml (23), but is unstable in water and is formulated as a lyophilized powder (stored refrigerated) that is reconstituted with 100% dehydrated ethanol to 33 mg/ml, then further diluted 10-fold with water for injection then administered by IV infusion over 1–2 h (4). Carmustine recently became commercially available in

Table V. Continued

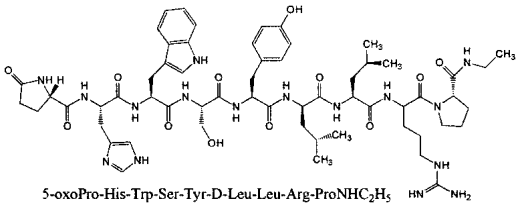
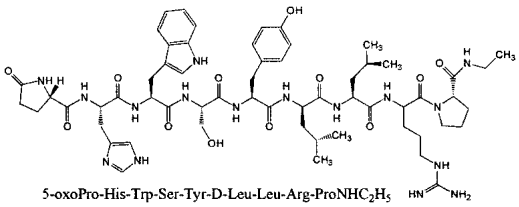
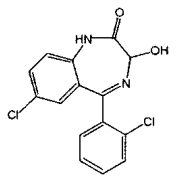
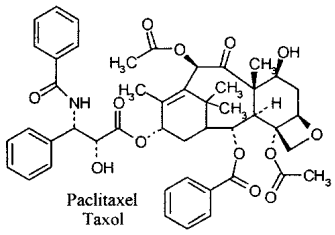
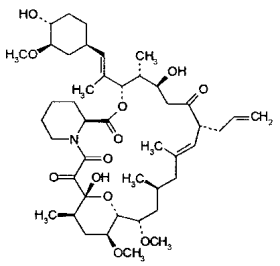
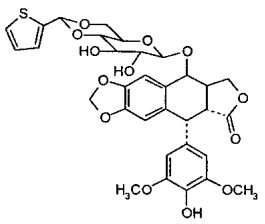
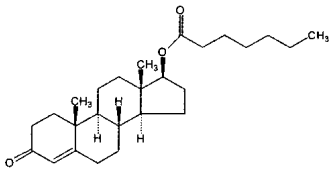
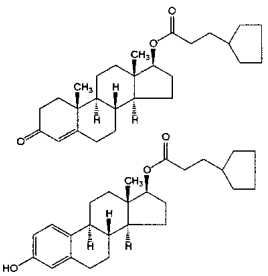
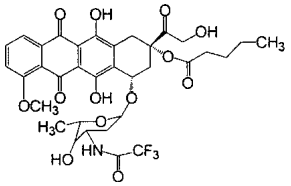
Molecule/ Trade Name/ Company/ Indication	Chemical structure	Formulation	Preparation	Administration
Leuprolide acetate I) Eligard/ Atrix Laboratories/ Prostate cancer	 5-oxoPro-His-Trp-Ser-Tyr-D-Leu-Leu-Arg-ProNHC$_2$H$_5$	1. 7.5 mg, 22.5 mg, or 30 mg Each strength utilizes the Atrigel Drug Delivery System. First syringe: poly(DL-lactide-co-glycolide) polymer dissolved in *N*-methyl-2-pyrrolidone (NMP). Second syringe: Leuprolide acetate powder. Eligard has 7.5 mg of leuprolide acetate, 160 mg of NMP, and 82.5 mg of polymer	1. Connect the two syringes then mix the contents of the two syringes.	1. SC Controlled release over 1 month (7.5 mg), 3 months (22.5 mg), or 4 months (30 mg)
II. Viadur/ Bayer	 5-oxoPro-His-Trp-Ser-Tyr-D-Leu-Leu-Arg-ProNHC$_2$H$_5$	2. 72 mg in Dimethyl sulfoxide (DMSO) using DUROS technology	2. Surgical implant of an osmotically driven pump of 4 mm by 45 mm.	2. SC implant Controlled release over 12 months
Lorazepam/ Ativan®/ Wyeth-Ayerst/ Anxiolytic, sedation		2–4 mg/ml PEG 400 at 18%, in Propylene glycol, Benzyl alcohol 2%	None for IM. For IV dilute with equal volume of saline, D5W, or lactated Ringer's.	IM/IV bolus at = 2 mg/min
Paclitaxel/ Taxol/ Bristol-Myers Squibb/ Antineoplastic	 Paclitaxel Taxol	Solution 6 mg/ml Cremophor EL 51%, Ethyl alcohol 49% (v/v)	Dilute with saline, D5W, or lactated Ringer's to 0.3–1.2 mg/ml.	IV infusion
Tacrolimus/ Prograf/ Fujisawa/ Immuno-suppressant		5 mg/ml Cremophor RH 60 20%, Ethyl alcohol 80%	Dilute 250- or 1000-fold into saline or D5W to 0.004–0.02 mg/ml	IV infusion
Teniposide/ Vumon/ Bristol-Myers Squibb/ Antineoplastic		50 mg/ml Cremophor EL 50%, Ethyl alcohol 42%, Dimethylacetamide 6%, Benzyl alcohol 30 mg/ml pH 5 (maleic acid)	Dilute with saline or D5W to 0.1–1 mg/ml	IV infusion over 30–60 min

Table V. Continued

Molecule/ Trade Name/ Company/ Indication	Chemical structure	Formulation	Preparation	Administration
Testosterone Enanthate/ Delatestryl/ BTG/ Hormone		200 mg/ml Sesame oil, chlorobutanol 5 mg/mL	None	IM
Testosterone Cypionate and Estradiol cypionate/ Depo-Testadiol/ Pharmacia & Upjohn/ Hormone		Testosterone Cypionate 50 mg Estradiol Cypionate 2 mg Cotton seed oil 874 ml Chlorobutanol 5.4 mg	None	IM
Valrubicin/ Valstar™ Medeva/ Antineoplastic		40 mg/ml Cremophor EL 50%, Ethyl alcohol 50%	Dilute with saline to 10.6 mg/ml	Intravesical instillation in the urinary bladder

controlled release Gliadel wafers composed of an anhydride copolymer with 7.7 mg of carmustine are surgically implanted during brain surgery (up to eight wafers to cover as much of the resection cavity as possible) and erode over 3 weeks (Ref. 3, see www.fda.gov/cder/foi/nda/2003/20-637S016_Gliadel_Approv.pdf).

The combination of propylene glycol and ethanol is commonly used to solubilize drugs. Phenobarbital, a sedative, hypnotic, and anticonvulsant, has an intrinsic water solubility of 1 mg/ml and two acidic pK_as of 7.3 and 11.8 (23) and is solubilized to 30–130 mg/ml in a cosolvent mixture of 68–75% propylene glycol and 10% ethanol at pH 9–10 (monosodium salt of phenobarbital) which is administered undiluted by either intramuscular or slow IV bolus injection (4). Pentobarbital sodium (Nembutal) at pH 9.5, phenytoin sodium at pH 10–12, and digoxin (Lanoxin) at pH ~7 are all solubilized in solutions with 40% propylene glycol and 10% ethanol and are administered undiluted by intramuscular injection (only rarely for digoxin due to injection site pain) or by slow intravenous bolus at ~1 ml per minute. Diazepam, a common skeletal muscle relaxant, has a basic pK_a of 3.4 (too low for pH adjustment) and is only slightly water-soluble (23), but the free base is solubilized in Valium to 5 mg/ml using a cosolvent of 40% propylene glycol and 10% ethanol without pH adjust. Melphalan hydrochloride, an antineoplastic agent, is formulated in Alkeran as a lyophilized powder that is reconstituted to 5 mg/ml with a supplied diluent of water, 60% propylene glycol, and 5% ethanol which is further diluted 10-fold with saline and then administered by IV infusion.

Polyethylene glycol 300 (PEG 300) and polyethylene glycol 400 (PEG 400) are generally considered to be among the safest organic cosolvents (51–53) and are very commonly used in preclinical *in vivo* pharmacokinetic and efficacy studies due to their solubilizing capabilities and safety. There are some commercial injectable formulations with PEG 300, but far fewer compared to propylene glycol and/or ethanol. Methocarbamil, a skeletal muscle relaxant, has solubility in water of 25 mg/ml (23) and is solubilized to 100 mg/ml in Robaxin using 50% PEG 300 which is administered undiluted intramuscularly using no more than 5 ml per injection site or by slow IV bolus at a maximum rate of 3 ml per minute. Robaxin can also be administered by IV infusion after a dilution of ≤25-fold using saline or dextrose 5%.

Glycerin is used infrequently in injectable formulations. Dihydroergotamine mesylate, used in the treatment of migraine headache, is formulated at 1 mg/ml in a pH 3.6 cosolvent mixture of 15% glycerin and 6% ethanol and is injected undiluted by either IV bolus, intramuscularly, or subcutaneously. Glycerin comprises 2.5% of the idarubicin formulation, Idamycin PFS, and is administered undiluted by IV infusion.

The water-soluble solvents PEG 400, DMA, and NMP are very effective solubilizing excipients, but are currently in only a few marketed injectable products that are all nonaqueous formulations.

Polysorbate 80 is a surfactant commonly used in protein parenteral formulations to minimize denaturation at the air–water interface. Polysorbate 80 is also sometimes used in injectable solution formulations of small molecules for the purpose of solubility enhancement due to micelle formation. Amiodarone hydrochloride, a cardiovascular drug with water solubility of 0.7 mg/ml and a tertiary amine with pK_a = 6.6 (23), is solubilized to 50 mg/ml in Cordarone by a combina-

Table VI. List of Water-Soluble Solvents and Surfactants in Commercially Available Injectable Formulations

Solvent	% in Marketed formulation	% Administered	Route of administration*	Selected examples
Cremophor EL	11–65	≤10	IV infusion	Paclitaxel
	50	18	Intravesical	Valrubicin
Cremophor RH 60	20	≤0.08	IV infusion	Tacrolimus
Dimethylacetamide (DMA)	6	≤3	IV infusion	Teniposide
Ethanol	5–80	≤6	SC	Dihydroergotamine
		≤10	IM	Phenytoin
		≤10	IV infusion	Paclitaxel
		≤20	IV bolus	Paricalcitol
Glycerin	15–32	≤15	IM, SC, IV	Dihydroergotamine
		≤2.5	IV infusion	Idarubicin
N-methyl-2-pyrrolidone	100 (diluent)	100	Subgingival	Doxycycline
(Pharmasolve)	100	100	SC	Leuprolide
PEG 300	≤60	≤50	IM, IV bolus	Methocarbamil
PEG 400	18–67	≤18	IM	Lorazepam
		≤9	IV bolus	Lorazepam
Polysorbate 80	0.075–100	≤4	IM	Chlordiazepoxide
(Tween 80)		12	IM	Vitamin A
		≤0.4	IV bolus	Amiodarone
		≤2	IV infusion	Docetaxel
Propylene glycol (PG)	10–80	≤80	IM	Lorazepam
		≤68	IV bolus	Phenobarbital
		≤6	IV infusion	Medroxyprogesterone
Solutol HS 15			IV	Diclofenac
	50	50	IV	Propanidid
	7	7	IV	Vitamin K_1

* IM, intramuscular; IV, intravenous; PEG, polyethylene glycol; SC, subcutaneous

tion of 10% polysorbate 80 and pH adjustment to 4.1 and is administered by intravenous infusion after a 25-fold dilution with dextrose 5%. Polysorbate 80 comprises 4% of the chlodiazepoxide formulation along with 20% propylene glycol and is injected undiluted intramuscularly. Calcitrol and doxercalciferol are formulated for intravenous bolus injection in Calcijex and Hectorol, respectively, at 1–2 μg/ml using an aqueous buffer with 0.4% polysorbate 80. In one case, docetaxel, 100% polysorbate 80 is used as the solubilizing vehicle, but is then diluted 50- to 100-fold prior to IV infusion.

Solutol HS 15 is a water-soluble non-ionic solubilizer that was developed for use in parenteral formulations with lipophilic drugs and vitamins (57). Solutol HS 15 is a mixture of ~70% lipophilic molecules consisting of polyglycol mono- and diesters of 12-hydroxystearic acid and ~30% hydrophilic molecules consisting of polyethylene glycol (Table III). Solutol HS 15 is in intravenous and oral formulations in various countries. In intravenous formulations, Solutol HS-15 is used at concentrations up to 50% to solubilize propanidid in Panitol (Cryopharma in Mexico), 7% to solubilize Vitamin K_1 (Sabex in Canada), and diclofenac (Argentina) (58). Solutol HS 15 is becoming more widely used and complies with the requirements of the German Pharmacopedia monograph (DAB) for Macrogol-15 hydroxystearate, and a US-DMF (drug master file) was also filed. Solutol HS 15 has also been used successfully in preclinical formulations in preparing supersaturated injectable formulations of water-insoluble molecules (59).

Organic Injectable Formulations

Molecules that are non-ionizable, lipophilic, and nonpolar are challenging to formulate due to their low water solubility and no effect of pH on solubility. Examples include paclitaxel, docetaxel, cyclosporin A, valrubicin, etoposide, teniposide, lorazepam, tacrolimus, testosterone enanthate, and haloperidol decanoate, and they are all solubilized in nonaqueous solutions composed entirely of organic solvent(s), which are usually but not always diluted prior to administration (Table IV).

Water-Miscible Organic Injectable Formulations

Propylene glycol, PEG 300, ethanol, Cremophor EL, Cremophor RH 60, and polysorbate 80 are the water-miscible solvents and surfactants in commercially available injectable formulations that are entirely organic. These solvents are normally used in combinations with each other, except in one case polysorbate 80 is used alone (docetaxel). These organic formulations are usually diluted at least 2-fold prior to IV bolus or IV infusion, but for intramuscular administration the propylene glycol–based formulation of lorazepam (Ativan) is administered undiluted.

The combination of Cremophor EL and ethanol is used to solubilize paclitaxel, teniposide, valrubicin, tacrolimus, and cyclosporin. Paclitaxel, a first-line cancer therapeutic, is very water insoluble and is solubilized in Taxol to 6 mg/ml with 51% Cremophor EL and 49% ethanol and is administered by IV infusion after a 5- to 20-fold dilution with dextrose 5% or lactated Ringer's. The final dosing formulation of Taxol is a micellar dispersion (60). Teniposide, an antineoplastic agent used to treat leukemia, is insoluble in water and is solubilized in Vumon to 10 mg/ml with 50% Cremophor EL, 42% ethanol, and 6% DMA and is administered by IV infusion after a 10-fold or a 100-fold dilution with saline or dextrose 5%.

Table VII. List of Oils Used in Commercially Available Parenteral Formulations

Oil	% Administered	Route of administration	Selected example
Castor oil	Mixture of castor oil/ ethanol/benzyl alcohol	IM	Fulverstrat
Cottonseed oil	100	IM	Testosterone cypionate Estradiol cypionate
Medium chain triglycerides	10–20%	IV infusion	Lipofundin MCT 10% Lipofundin MCT 20%
Sesame oil	100	IM	Haloperidol decanoate Testosterone
Soybean oil	10%	IV bolus	Propofol
	10–20%	IV infusion	Intralipid, Liposyn III
Safflower oil	5–10%	IV infusion	Liposyn II

Valrubicin, an antineoplastic agent used to treat carcinoma of the urinary bladder, is relatively insoluble in water (2) and is solubilized in Valstar to 40 mg/ml with 50% Cremophor EL and 50% ethanol and is diluted 4-fold with saline prior to intravesical instillation in the urinary bladder. Tacrolimus, an immunosuppressant used to prevent rejection of liver and kidney transplants, is insoluble in water and is solubilized in Prograf to 5 mg/ml with 20% Cremophor RH 60 and 80% ethanol and is administered by IV infusion after a 250-fold or a 1000-fold dilution with saline or dextrose 5%. Cyclosporin A is solubilized in Sandimmune to 50 mg/ml with 65% Cremophor EL and 35% ethanol and is administered by IV infusion after a 20-fold or a 100-fold dilution with saline or dextrose 5%.

Lorazepam, a benzodiazepine used for sedation and epilepsy, has a water solubility of only 0.08 mg/ml (23) and is solubilized in Ativan to 2–4 mg/ml with propylene glycol and 18% PEG 400 and is administered either undiluted intramuscularly or by IV bolus after a 2-fold dilution with saline, dextrose, or lactated Ringer's. Etoposide, a sparingly soluble antineoplastic agent (2), is solubilized in VePesid to 20 mg/ml with 60% PEG 400, 30% ethanol, and 8% polysorbate 80, and is administered by IV infusion after a 50- to 100-fold dilution with saline or dextrose 5%. Docetaxel, a first-line therapeutic to treat breast and small cell lung cancer, is practically insoluble in water (2) and is solubilized in Taxotere to 40 mg/ml in polysorbate 80, and is diluted 4-fold with the supplied diluent of 13% ethanol in water, then further diluted to 0.3–0.74 mg/ml with saline or dextrose 5% prior to administration by IV infusion.

Oily Injectable Formulations

Vegetable oils can solubilize very lipophilic drugs and are administered by intramuscular injection providing a depot for sustained drug delivery over 2–4 weeks as the oil diffuses within the intramuscular tissues. The oils in commercially available solution injectable formulations are listed in Table VII and include castor oil, cottonseed oil, sesame oil, soybean oil, and safflower oil. Haloperidol decanoate is the long-acting, water-insoluble decanoate ester prodrug form of haloperidol, a drug to treat psychotic disorders, and is solubilized to 50 and 100 mg/ml in sesame oil which is administered intramuscularly through a 21-gauge needle in which the maximum volume per injection site should not exceed 3 ml. The peak plasma concentrations occur at about 6 days after injection and thereafter decline with a half-life of about 3 weeks, thus requiring monthly individualized maintenance doses. Testosterone enanthate, a prodrug of testosterone and used to treat hormone deficiency, is solubilized in Delatestryl at 200 mg/ml in sesame oil and is administered intramuscularly approximately every 2 weeks. Testosterone cypionate and estradiol cypionate are cosolubilized in cottonseed oil in Depo-Testadiol for intramuscular injection. Fulvestrant is solubilized in a mixture of castor oil, ethanol, and benzyl alcohol in Faslodex for intramuscular injection.

Emulsion Injectable Formulations

Oil-soluble molecules are generally neutral, uncharged, and nonpolar, but can be formulated for intravenous administration in an oil-in-water emulsion because the drug partitions into the oil phase. A typical emulsion is composed of water with 10–20% soybean and/or safflower oil, 2% glycerol, 1% egg lecithin, and at pH 7–8 and is injected by either IV bolus or IV infusion. Total parenteral nutrition (TPN) formulations are lipid emulsions that are administered by intravenous infusion as nutritional supplements, and the commercially available emulsions include Intralipid (10–20% soybean oil), Liposyn (10–20% safflower oil), and Lipofundid MCT/TCL (5–10% soybean oil and medium-chain triglycerides). In Europe and Japan, there are multiple drug-containing emulsions commercially available, and they include diazepam, PGE_1, dexamethasone palmitate, and flurbiprofen (61). The only commercially available emulsion formulation in the United State is Diprivan in which propofol, a water-insoluble phenol-containing sedative, is solubilized to 10 mg/ml in an emulsion composed of 10% soybean oil and is administered either by IV bolus or IV infusion.

Cyclodextrin-Containing Injectable Formulations

Increased water solubility through molecular complexation with cyclodextrins has advantages over the cosolvent approach because upon dilution, a 1:1 complex between a cyclodextrin and a drug molecule will not precipitate, but a drug dissolved in a cosolvent can precipitate upon dilution.

Alprostadil, also known as prostaglandin E_1 (PGE_1), is naturally occurring and is used in the treatment of erectile dysfunction. Alprostadil is solubilized by forming an inclusion complex with α-cyclodextrin and is marketed as a lyophilized powder, Edex, which is reconstituted with saline to 10–40

μg/ml and injected intracavernously. Itraconazole is water-insoluble and is solubilized in Sporanox to 10 mg/ml in an aqueous pH 4.5 solution with 40% hydroxypropyl-β-cyclodextrin and is administered by intravenous infusion after a 2-fold dilution with saline. Hydroxypropyl-β-cyclodextrin is also used to solubilize mitomycin in the generic product Mitozytrex (MitroExtra) (3).

The newest cyclodextrin to be commonly used is sulfobutylether-β-cyclodextrin (Captisol, www.cydexinc.com, Overland Park, KS, USA, Table III). Captisol is very safe (37,62), chemically stable, water-soluble, and is an excellent solubilizing drug delivery technology for molecules in which it forms an inclusion complex. An aqueous solution with 12% w/v Captisol is isotonic, but formulations can contain as much as 30% w/v Captisol. Ziprasidone mesylate, a rapid-acting antipsychotic, a weak base with a pK_a of 6.5 and an intrinsic water solubility of 0.3 μg/ml, is solubilized in Geodon to 20 mg/ml with ~29% w/v Captisol and is administered by intramuscular injection. Ziprasidone mesylate and Captisol form a 1:1 complex in which the benzisothiazole group of ziprasidone is positioned within the cavity of a Captisol molecule (63). Geodon injectable formulation was initially approved in 2000 in Sweden (64,65). Voriconazole is a weakly basic triazole antifungal that is solubilized in Vfend to 10 mg/ml with ~16% w/v Captisol and is administered by IV injection after a further 2-fold dilution with IV fluids (2).

Aqueous Dispersion Injectable Formulation

Phytonadione (Vitamin K_1) is a non-ionizable water-insoluble viscous liquid used in Vitamin K deficiency, is solubilized in AquaMEPHYTON to 2 or 10 mg/mL in an aqueous dispersion with 7% polyoxyethylated fatty acid derivative, 37 mg/mL dextrose, and 0.9% benzyl alcohol at pH 3.5–7, and is administered undiluted by subcutaneous or intramuscular injection. If IV administration is unavoidable, the rate of injection should not exceed 1 mg per minute.

Liposome Injectable Formulations

Liposomes are closed spherical vesicles composed of outer lipid bilayer membranes and an inner aqueous core and with an overall diameter of <100 μm. Depending on the level of hydrophobicity, moderately hydrophobic drugs can be solubilized by liposomes if the drug becomes encapsulated or intercalated within the liposome. Hydrophobic drugs can also be solubilized by liposomes if the drug molecule becomes an integral part of the lipid bilayer membrane, and in this case, the hydrophobic drug is dissolved in the lipid portion of the lipid bilayer. Water-soluble molecules reside within the aqueous inner core and are released either as the liposome is eroded *in vivo* or by leakage. Liposomal formulations provide several therapeutic advantages over the native drug formulations, including improved pharmacokinetics (increased *in vivo* half-life of the drug), enhanced efficacy, and reduced toxicity. Liposomes preferentially bind to target cells such as fungal and tumor cells as opposed to mammalian host cells, thus higher drug exposure to the target cells improves efficacy, and the limited exposure to host cells decreases the toxicity. A typical liposome formulation contains water with phospholipid at ~5–20 mg/ml, an isotonicifier, a pH 5–8 buffer, and with or without cholesterol. Liposomes are injected either by IV infusion or intrathecally.

There are currently at least four commercially available liposomal products for injection: amphotericin B (Table IV), cytarabine, daunorubicin, and doxorubicin. Of these, only amphotericin B is solubilized by liposomal encapsulation; the other three drugs are water-soluble and are liposomal formulated for pharmacokinetic reasons. Amphotericin B, an antifungal, contains both a primary amine and a carboxylic acid group, but the water solubility of the anion (pH 11) or cation (pH 2) is only ~0.1 mg/ml (23). Amphotericin B is solubilized to 5 mg/ml by liposomal intercalation and becomes an integral part of the lipid-bilayer membrane. The commercially available Amphotericin B liposomal product, Ambisome, is a lyophilized cake that is reconstituted with water to a 4 mg/ml translucent liposomal suspension containing 18 mg/ml HSPC (hydrogenated soy phosphatidylcholine), 7 mg/ml DSPG (distearoylphosphatidylglycerol), 4 mg/ml cholesterol, 0.05 mg/ml α-tocopherol, 75 mg/ml sucrose, and 2 mg/ml disodium succinate buffer (pH 5–6). The reconstituted Ambisome is then filtered through a provided 5-μm filter and diluted with dextrose 5% to ~1 mg/ml and administered by IV infusion. Another amphotericin B product, Abelcet, is a lipid complex that is an opaque suspension at 5 mg/ml with 3.4 mg/ml DMPC (L-α-dimyristoylphosphatidylcholine), 1.5 mg/ml DMPG (L-α-dimyristoylphosphatidylglycerol), 9 mg/ml sodium chloride, and buffered to a pH of 5–7. Abelcet is diluted with dextrose 5% to 1–2 mg/ml and administered by IV infusion. The amphotericin B lipid-based products have an *in vivo* elimination half-life of 100-173 h (2). However, the liposomal Ambisome has significantly lower incidence of nephrotoxicity and infusion-related reactions compared to the lipid complex Abelcet which allows for higher doses of amphotericin B when using Ambisome. Thus, liposomal encapsulation of amphotericin B not only increases its solubility, but also decreases its toxicity and also increases the *in vivo* half-life.

Organic Solvents in Controlled Release and Other Applications

N-Methyl-2-Pyrrolidone in a Polymeric Gel: Subcutaneous or Local Injection

N-methyl-2-pyrrolidone (NMP, Pharmasolve) is a very strong solubilizing agent and is currently in only a few commercially available pharmaceutical products. Leuprolide acetate is used in the treatment of prostate cancer and is solubilized in a solution composed of 55–66% NMP and 34–45% poly(DL-lactide-co-glycolide) in an *in situ* controlled release gel, Eligard, that is injected subcutaneously as a liquid. Upon administration of ~0.25–0.50 ml of the liquid formulation, the NMP diffuses away from the injection site leaving a polymeric gel that provides a depot of drug that is released over 1 to 6 months as the gel erodes or dissolves. Eligard 7.5 mg and Eligard 22.5 mg have been commercially available since 2002 and are 1-month and 3-month controlled release products, respectively. Eligard 7.5 mg delivers 7.5 mg of leuprolide acetate dissolved in 160 mg of NMP with 82.5 mg of poly(DL-lactide-co-glycolide) as a 50:50 molar ratio. Eligard 30 mg is a 4-month controlled release product and was approved by the

FDA in February 2003. Eligard 45 mg is a 6-month controlled release product and is in Phase III clinical trials (55,56). Eligard uses the Atrigel drug delivery system, which is a two-syringe set-up where syringe A contains the polymer poly(DL-lactide-co-glycolide) or poly(DL-lactide) dissolved in NMP, and syringe B contains solid drug. Upon coupling the two syringes, the liquid in syringe A is injected into syringe B and repeatedly mixed to complete dissolution, and then the viscous liquid is administered either subcutaneously or subgingivally (Ref. 3, see www.atrixlabs.com, Atrix Laboratories, Inc., Fort Collins, CO, USA).

The Atrigel drug delivery system is also used in three dental products. Doxycycline hyclate, a water-soluble antibiotic, is available as a 7-day controlled release system, Atridox, composed of 100 mg/ml doxycycline hyclate in NMP with 37% poly(DL-lactide) that is a solution upon subgingival administration, but solidifies upon contact with the crevicular fluid and is used to treat peridontal disease. Two similar drug products containing 50 mg/ml doxycycline hyclate, and also in NMP with 37% poly(DL-lactide), are Atrisorb-FreeFlow and Atrisorb-D FreeFlow, which are used for peridontal tissue regeneration (56) in which the physician first applies demineralized bone matrix to the treated area, then administers the Atrisorb-FreeFlow drug product that upon spreading forms an *in situ* gel.

Dimethyl Sulfoxide in a Subcutaneous Implant

Dimethyl sulfoxide was recently added to the monograph of pharmaceutical excipients (26) and is the solubilizing solvent in a subcutaneously implanted, osmotically driven pump that delivers drug for up to 1 year. The DUROS implant was developed by Alza Corporation, licensed to Durect Corporation for selected fields, and became commercially available in 2000 in Viadur to deliver leuprolide acetate. The implant is a multicomponent device comprising a 4 mm × 45 mm titanium alloy cylindrical reservoir that contains at the inlet end a polyurethane rate-controlling membrane. The inner reservoir of Viadur consists of osmotic tablets that swell to push an elastomeric piston down the cylinder that pushes a solution of 72 mg of leuprolide acetate dissolved in 104 mg of DMSO through a polyethylene diffusion moderator at the outlet end. The entire Viadur device, weighing about 1.1 g, is surgically inserted subcutaneously in the inner aspect of the upper arm. After 12 months the implant must be removed and, if desired, replaced with another implant to continue therapy.

Dimethyl Sulfoxide in Intravesical Instillation

DMSO is the active ingredient in Rimso-50, which is a 50/50 mixture of DMSO and water, and is instilled intravesically for the treatment of interstitial cystitis. Instillation of 50 ml of Rimso-50 into the bladder may be accomplished by an aseptic syringe or by a catheter (2). This formulation is not for intravenous or intramuscular injection. A side effect is a garlic-like taste that may last for hours as well as an odor of the breath and skin due to the presence of DMSO metabolites.

STRATEGY OF FORMULATION APPROACHES

Table VIII is a flow chart of a suggested order of solubilization approaches for both injectable and oral formulations arranged in a "simple to more complex" manner. The salt form of the drug can have an impact on the solubility but is not included in this discussion.

Intravenous Injection

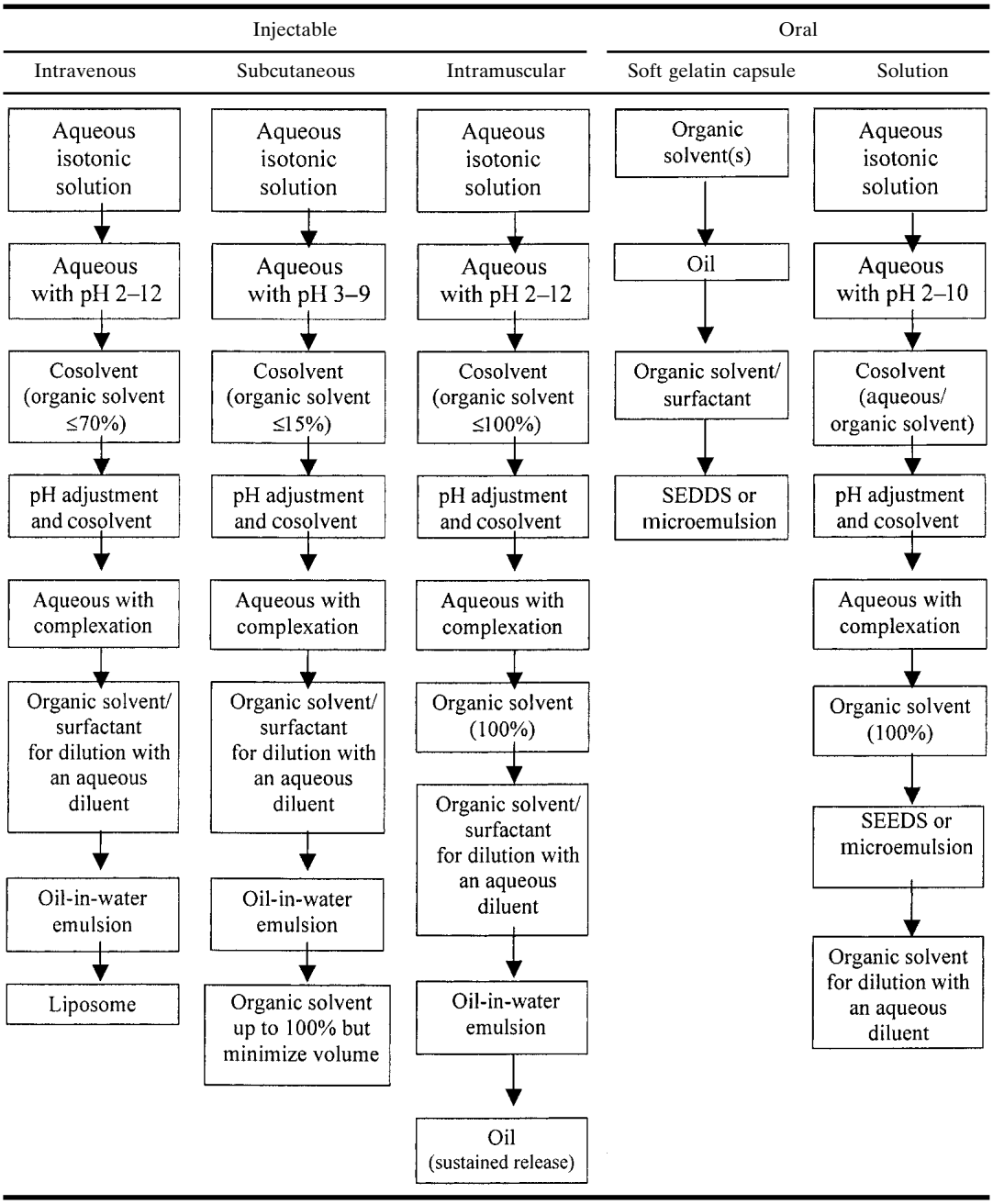
The ideal immediate-release injectable formulation is aqueous and isotonic with physiological fluids such as saline, dextrose 5%, or lactated Ringer's and with pH ~7. If the drug is not soluble in neutral pH water, the next choice is to increase solubility by changes in solution pH and/or the addition of a water-soluble organic solvent (i.e., a cosolvent). Knowledge of the drug's pK_a(s) is very useful, for only ionizable drugs can be solubilized by pH modification. Bolus intravenous formulations can range in pH from 2–12, but infusion formulations are normally limited to pH 2–10. If the drug is not solubilized sufficiently by pH modification, the next choice is to increase solubility by using a water-soluble organic solvent. The organic solvents in bolus intravenous formulations include ethanol, glycerin, PEG 300, PEG 400, and propylene glycol with the upper amount being 20% for ethanol and ~50% for the others. The organic solvents in intravenous infusion formulations include DMA, ethanol, glycerin, PEG 300, PEG 400, and propylene glycol with the upper amount being 3% for DMA, 15% for glycerol, and ~10% for the others. The combination of both pH modification and cosolvent can be a very powerful solubilization strategy and is quite useful in the preclinical setting when one does not have much time/resources to develop an optimized formulation (43).

If the drug is not solubilized by aqueous pH-modification or in cosolvents, the next choice is to increase aqueous solubility by complexation. The preferred complexing agents are cyclodextrins and their derivatives, and typically only those drugs with an aromatic ring or a nonpolar side chain are solubilized by cyclodextrin complexation. If complexation alone is insufficient, then a combination of complexation and pH modification (66) or/and cosolvent may be used.

If the drug is not solubilized by pH modification, cosolvents, complexation, or combinations of these, the drug is considered "challenging." Surfactants are used to solubilize some of the most water-insoluble drugs, and the formulations are usually concentrated drug solutions in a completely organic solvent(s) that is diluted prior to intravenous administration, such as those listed in Table II. The surfactants for intravenous infusion formulations include Cremophor EL, Cremophor RH 60, and polysorbate 80. The solubilizing solvent is typically a mixture of surfactant and solvent(s) such as cremophor/ethanol, cremophor/ethanol/DMA or polysorbate 80/PEG 300/ethanol, but neat surfactant may also be used such as polysorbate 80 to solubilize docetaxel. The upper limit administered *in vivo* is <10% for the cremophors and up to 25% polysorbate 80.

Drugs that are not soluble by cosolvents, pH modification, or complexation but are soluble in oils can be formulated for intravenous administration by employing an oil-in-water emulsion. Emulsion typically contain 10–20% oil and an oil-soluble drug partitions into the oil phase. This formulation strategy is rarely used for a commercial product. However, emulsions can be useful in the preclinical setting where an extemporaneous emulsion is prepared by slowly adding a concentrated solution of drug in an organic solvent to an emulsion with constant stirring (14).

Table VIII. Flow Chart of Suggested Order of Solubilization Approaches for Injectable and Oral Liquid Formulations



Liposome formulations can be used as a means to solubilize some drugs for intravenous administration, but this solubilization strategy is complex and liposomes are normally not used for solubility enhancement but for pharmacokinetic purposes.

Water-insoluble drugs that are not solubilized by any of the above techniques or combinations of techniques are considered "quite challenging." In these cases, because the equilibrium solubility is below the target formulation concentration, a supersaturated solution may be achievable in which case the drug stays in solution for a long enough period of time for handling and dosing. The typical approach is to dissolve the drug in a preconcentrated organic solution with/without surfactant and slowly add this solution to an aqueous-based injectable solution. To achieve supersaturation, the final injected formulation usually, but not always, contains a surfactant(s) that is either initially in the concentrated drug solution or in the diluent. This technique can be difficult to commercialize due to complexity. However, this supersaturation technique is very useful in formulating water-insoluble drugs, and many parameters can be varied such as the preconcentrate drug concentration, preconcentrate solvent(s), diluent composition, and the mode of mixing the preconcentrate and the diluent. A novel example of combining pH-modification, cyclodextrin complexation, supersaturation, as well as *in situ* chemical conversion in an intravenous formulation is the water-insoluble campothecin analog, DB-67, which was not solubilized by any of the usual techniques (67).

A successful intravenous formulation of DB-67 at 2 mg/ml was achieved by dissolving the carboxylate E-ring opened analog in an alkaline aqueous solution at 20 mg/ml which was added slowly to an acidified aqueous solution containing 20% SBE-β-CD in which the lactone was generated *in situ* in solution at a supersaturated concentration, but stayed in solution for >3 days. For long-term storage, the supersaturated solution was lyophilized, and the powder was reconstituted prior to injection.

Subcutaneous Injection

The strategy of solubilizing a drug for subcutaneous administration is similar for intravenous administration, but with more restrictions. The most significant restrictions are the need for a low viscosity formulation, a reduced injection volume to less than 2 ml, and more restrictions on both the pH range and the amount of cosolvent due to slower diffusion away from the injection site. The generally accepted pH range is 2.7–9.0, and for immediate release the accepted upper limit of cosolvent is <15%. However, undiluted NMP is injected subcutaneously, but the volume is minimized to <0.5 ml.

Intramuscular Injection

The strategy of solubilizing a drug for intramuscular administration is similar for intravenous administration, but with fewer restrictions. For intramuscular administration, the pH range is similar to intravenous and is pH 2–12, but there will be some stinging at the injection site when using the extremes of pH. For intramuscular administration, the amount of cosolvent is generally less restrictive than intravenous and can be as high as 100% organic. When using an oil to solubilize a drug for intramuscular administration, the oil formulation is injected undiluted and normally provides a depot of drug that released over time (up to months).

Oral Administration

A solubilized dosage formulation for oral administration is normally contained within a capsule or is a measurable oral solution in a bottle.

Capsules

The development of a solubilized oral formulation in a capsule is normally driven by the desire to either increase or make reproducible the oral bioavailability of a poorly water-soluble molecule compared to a solid oral dosage form. The preferred water-soluble organic solvents for soft gelatin capsules are PEG 400 and propylene glycol. Ethanol can also be used in capsules, but the amount is limited to <15% because ethanol can diffuse out of a capsule due to its volatility. The water-insoluble solvents in commercially available solubilized oral formulations include the long-chain triglycerides peanut oil, corn oil, soybean oil, sesame oil, olive oil, peppermint oil, hydrogenated vegetable oils, hydrogenated soybean oil, and the medium-chain (C_8/C_{10}) caprylic/capric triglycerides derived from coconut oil and palm seed oil. If solubility and/or oral bioavailability is still not sufficient, the next level of complexity is to add a surfactant such as TPGS, Cremophor EL, Cremophor RH 40, TWEEN 80, SPAN 80, Solutol HS-15, Softigen 767, Labrafil M-1944CS, or Labrafil M-2125CS. If solubility and/or oral bioavailability is still not sufficient, the next level of complexity is a self-emulsifying drug delivery system that contains a polar solvent, an oil, a surfactant, and a cosurfactant.

Oral Solutions

Measurable solution formulations for oral dosing include pediatric/elderly formulations, dose reduction compared to the available solid oral dosage form(s), and cold remedies. The development of pediatric formulations is beyond the scope of this review, but can also include suspensions, powders, and other formulation types as well as the very important aspect of taste-masking. The requirements of a successful oral solution are not only oral bioavailability, but also acceptable chemical stability and physical properties as well as acceptable taste.

Oral solution formulations can be either aqueous, aqueous/organic, or entirely organic. Therefore, all of the excipients discussed in this review, oral and injectable, can be used in an oral dose solution. If solubility and oral bioavailability are sufficient in an aqueous or aqueous/organic solvent, then an aqueous-based solution formulation may be desirable. If water solubility is limited and oral bioavailability from a solid oral dosage form is low, then an organic solvent–based solution formulation may be needed.

FUTURE TRENDS AND PROSPECTS

Even though there are many available excipients to increase the solubility of poorly water-soluble drugs, there is still a need for more acceptable excipients and also to better understand how these excipients actually perform *in vivo*. The recent approval of products with "new" excipients such as the complexing agent sulfobutylether-β-cyclodextrin, the organic solvent NMP, and the surfactant TPGS are encouraging examples of emerging solubilizing excipients in parenteral (68) and oral medications. As more water-insoluble drugs are discovered through modern screening techniques, the need for significant formulation efforts in both preclinical and clinical development will increase.

The use of polymer-based capsules, such as hydroxypropyl methylcellulose or polyvinylalcohol hard capsules, within the pharmaceutical industry is likely to begin soon. Polymer-based capsules offer the advantages of potential controlled release as well as the intriguing potential to control closely the size, shape, and dimensions of the capsule. Enteric coating of soft gelatin (69) and HPMC capsules (17) also offers the possibility of intestinal targeting.

It would be beneficial to the formulation scientist to have more water-soluble organic solvents as potential vehicles. The currently used, preferred choices of propylene glycol, ethanol, and polyethylene glycols suffer from lack of solubilizing powers in many instances. The water-soluble solvent NMP will likely be used more frequently because it has excellent solubilizing powder and is low viscosity, which is of practical importance in using fine-gauge needles or microcatheters. DMSO was recently added to the monograph of pharmaceutical excipients and may be used more often. Other solvents have been considered, such as dimethyl isosorbide (70), glycofurol, Solketal, glycerol formal, acetone, tertrahydrofurfuryl alcohol, diglyme, and ethyl lactate, but are used mainly in

the preclinical setting (71) or in veterinary products. The solvent Transcutol is purified diethylene glycol monoethyl ether and is a powerful solubilizer that is used in some European products such as the oral drops Lysanxia and the oral solutions Pilosuryl and Urosiphon as well as in some veterinary injectable products such as Tolfedine and Vitamin E (72).

As more water-insoluble drugs are discovered, the need for lipid-based formulations or colloidal carriers such as solid lipid nanoparticles will increase for both oral and injectable formulations (73,74). Oral formulations of long-chain and medium-chain triglycerides will likely be used more often in all phases of development: preclincal, clinical, and commercial. Shorter chain triglycerides such as triacetin and tributyrin can solubilize many drugs and could potentially be used more. Lipids can be transported *in vivo* via the lymphatic system, and research to understand the contribution of lymphatic transport to oral bioavailability is ongoing (75,76).

Surfactants are quite useful excipients when used correctly, but are often the "last resort" if simpler organic solvents and pH changes are insufficient. The commonly used surfactants cremophors, polysorbates, Labrafils, TPGS, and Span 20 are proven useful but with limitations. Other surfactants that are currently used less commonly such as Solutol HS-15 (77) and the Gellucires and Labrasols can solubilize many drugs and will likely be used more frequently. The Gellucires and Labrasol are similar to the Labrafils and are well-defined mixtures of mono-, di-, and triglycerides and mono- and di-fatty acid esters of polyethyleneglycol with fatty acid compositions of C_{12} (Gellucire 44/14), C_{16}-C_{18} (Gellucire 50/13), and C_8–C_{10} (Labrasol). The use of surfactants could benefit from a better understanding of supersaturation phenomenon and its practical applications. Surfactants have also been shown to improve the oral absorption of highly polar and water-soluble macromolecules such as vancomycin (78).

Controlled release systems that are solvent-based will hopefully expand in their commercial success. The SABER delivery system, developed by Southern Biosystems, Inc. (79) and Durect Corporation, Cupertino, CA, USA (80), uses the water-insoluble, highly viscous, liquid sucrose acetate isobutyrate (SAIB) that is dissolved in low-viscous solvent such as NMP, ethanol, benzyl benzoate, or Miglyol 810 (medium-chain caprylic/capric triglyceride) along with the active ingredient. Upon subcutaneous or intramuscular injection, the SAIB forms an adhesive, biocompatible, and biodegradable depot that releases the entrapped active ingredient over a tailored time period of a few day to 3 months or more after a single injection. The SABER delivery system is undergoing clinical evaluation and can also be applied to oral, dermal, and other routes of administration.

Understanding how excipients perform *in vivo* is a key aspect of their ultimate success. Certain excipients are not "inert" but are "functional excipients" and can alter metabolism and/or transport activities. For example, a Pluronic block copolymer is undergoing Phase II clinical evaluation for its ability to modify cellular distribution by inhibition of the P-gp drug efflux transport system and is a functional excipient in a formulation with doxorubicin to increase distribution to solid tumors (81). Understanding how excipients improve oral bioavailability will depend partially on determining how excipients perturb physiological functions including passive diffusion and transport systems such as P-gp (82,83). Understanding how excipients affect the passive and lymphatic absorption of poorly water-soluble drugs will assist in designing better oral formulations. The ability of scientists to determine whether improved *in vivo* performance is due to solubility enhancement alone or in combination with physiological perturbations will allow for a more mechanistic understanding of formulation and excipient function(s).

CONCLUSIONS

Drug delivery has matured in the last few decades and is now recognized as an integral part of drug discovery and development (84–86), with current emphasis on designing favorable physicochemical properties into new chemical entities (87–89) and identifying the most favorable salt form (90). However, the trend to discover and develop small molecule therapeutics that bind to a chosen enzyme has resulted in more lipophilic, hydrophobic, and water-insoluble new drug candidates. Therefore, formulation development/optimization, drug solubilization, and drug delivery will continue to be areas of active research and development, with encouragement by current and future commercial successes.

ACKNOWLEDGMENTS

The author thanks Richard Dunn of Atrix Laboratories, Inc., Gerold L Mosher, Diane O, Thompson, and Karl W. Strohmeier of CyDex, Inc., Jennifer Lee and Peter Cade of Croda, Inc., Carey M. Boyum of Lipscomb Chemical Company, Inc. (Long Beach, CA, USA, representing Gattefosse, Inc., Cedex, France), Barbara A. Pagliocca of Sasol North America, Inc. (Westwood, NJ, USA), and Brendan O'Leary of BASF, Inc., for information on their specialty solubilizing excipients and drug delivery systems. The author also thanks Tamara L. Smith of Shionogi Qualicaps, Inc. (Whitsett, NC, USA), for information on hydroxypropyl methylcellulose capsules and Missy Lowery of Capsugel (Greenwood, SC, USA, a division of Pfizer, Inc.) for information on DBcaps capsules for double-blinded clinical trials. The author also thanks Terry Dahl, Reza Oliyai, and Taiyin Yang of Gilead Sciences, Inc., and Ngoc-Anh T. Nguyen for their careful review of this manuscript, support, encouragement, and helpful suggestions.

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