

glycol (PG), propylene glycol monoester of medium chain fatty acids (Capmul PG), dimethylsulfoxide (DMSO), and in different combinations of these cosolvents at four different temperatures. The degradation of the drug was monitored by HPLC and was found to be catalyzed not only by general but also by specific acid and base and followed first-order kinetics. The  $t_{90}$  (time for 90% of the drug remaining intact) in pure cosolvent was 25–50 times higher than that in water or semi-aqueous vehicles. Figure 4 shows an Arrhenius plot of the observed rate constants of SarCNU in the solvent mixtures. There was no significant difference in the slopes for the different solvents, suggesting similar degradation mechanism of SarCNU in all solvent mixtures. Furthermore, the order of stabilization by these solvents was Capmul PG > /EtOH> /PE> /PG> /WPE> /water, which was in agreement with decreasing the polarities of the vehicles. The greatest SarCNU stability, as measured by the degradation rate constant derived  $t_{90}$ , was observed with Capmul PG as shown in Table 4. Another example where the degradation was significantly reduced in the nonaqueous solvents is described for Eptifibatide, a peptide compound used as an inhibitor of platelet receptor glycoprotein (42). The use of cosolvent to help in solubilization may not, however, lead to favorable stability outcome at all the times. Trivedi, et al, (43) showed that as the fraction of organic solvents was increased, the degradation of zileuton also increased because of the solvolysis of the drug by the cosolvents used.

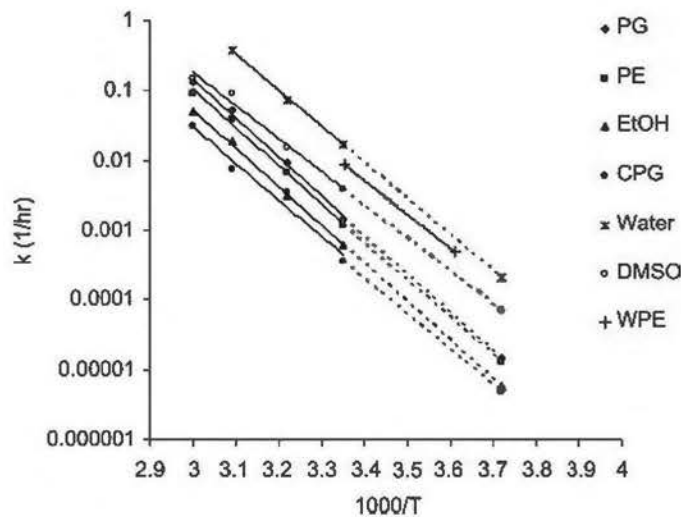


Figure 4 Stability behavior of SarCNU in the presence of various cosolvent.

Table 4 Degradation of SarCNU in the Presence of Various Cosolvent Mixtures

Solvent	$t_{90}$ (days)	
	Room temperature (25 °C)	Refrigeration (4 °C)
Water	0.25	5.90
Water + propylene glycol + EtOH	0.50	8.96
DMSO	1.14	19.03
Propylene glycol	2.92	77.78
Propylene glycol + EtOH	3.64	89.50
EtOH	7.29	199.52
Capmul PG	12.50	242.57

Source: From Ref. 41.

**Table 5** Examples of Marketed Injectable Products Containing Cosolvent Mixtures

Generic name	Trade name	Predominant cosolvent(s) in marketed vehicle
Carmustine	BICNU	100% ethanol
Diazepam	Valium	Propylene glycol 40% Ethyl alcohol 10%
Digoxin	Lanoxin	Propylene glycol 40% Ethyl alcohol 10%
Melphalan	Alkeran	Propylene glycol 60% Ethyl alcohol 5%
Methocabamol	Robaxin	Polyethylene glycol 50%
Oxytetracycline	Terramycin	Propylene glycol 67 75%
Paricalcitol	Zemplar	Propylene glycol 30% Ethyl alcohol 20%
Phenobarbital Na	Nembutal	Propylene glycol 40% Ethyl alcohol 10%
Phenytoin Na	Dilantin	Propylene glycol 40% Ethyl alcohol 10%
Teniposide	Vumon	<i>N,N</i> dimethylacetamide 6% Cremophor 50% Ethyl alcohol 40%
Docetaxel	Taxotere	Polysorbate 80 100%

Source: From Refs. 44 and 45.

Examples of drugs marketed in water-miscible systems include digoxin, phenytoin, diazepam and others as shown in Table 5 (44,45). These injections are formulated in a water-miscible system containing glycols and alcohol and adjusted to a suitable pH. Other cosolvents used in the past included glycerin in deslanoside, dimethylacetamide in reserpine and dimethylsulfoxide in chemotherapeutic agents undergoing clinical testing. Propylene glycol is used most frequently as a cosolvent, generally in concentrations of 40%. Although such systems are stable in individual vials, care must be exercised on administration. For example, phenytoin is dissolved as the sodium salt in a vehicle containing 40% propylene glycol and 10% ethanol and adjusted to a pH of 12 with sodium hydroxide. However, if this solution is added to a large-volume IV solution and the pH is lowered to a value close to the  $pK_a$  of the drug ( $pK_a = 8.3$ ), precipitation of the drug can occur. This is due to the fact that in aqueous systems at pH below 11, the amount of undissociated phenytoin exceeds its solubility.

To be used as solubility/stability enhancer in injectable products, the cosolvent must have certain attributes such as it should be nontoxic, compatible with blood, nonsensitizing, nonirritating and above all physically and chemically stable and inert. Many cosolvent formulations contain high concentrations of organic solvent and most are diluted prior to injection, however, some may be injected directly and in that case, care must be taken that the rate of injection remains slow.

**Surfactants as solubilizers** The ability of surfactants to enhance the solubility of otherwise poorly water-soluble compounds in aqueous solution is widely known and used in many injectable formulations. Surfactants are effective solubilizing agents because of their wetting properties and association tendencies as they are able to disperse water-insoluble substances. Surfactants are also used very widely in the biotechnology area for otherwise water-soluble monoclonal antibodies and other proteins and polypeptides, but the primary goal of using surfactant in these products is to minimize hydrophobic interaction related aggregation and not necessarily for the enhancement of solubility. This aspect will be discussed in detail in other chapters.

Surfactants can be either nonionic or ionic (i.e., the ability to lower surface tension rests with the anion or cation in the molecule). In nonionic surfactants, the head groups contain no charged moieties and their hydrophilic properties are due to the presence of hydroxyl groups. Nonionic surfactants are most frequently used in pharmaceutical systems because of their compatibility with other surfactants, stability, and relatively low toxicity. Some examples of

water-soluble nonionic surfactants include long-chain fatty acid analogs such as fatty alcohols, glyceryl esters, and fatty acid esters. Among the most widely used water-soluble nonionic surfactants in injectable products are polyethylene oxide (PEO) sorbitan fatty acid esters, or Polysorbates.

In anionic surfactants, the head groups are negatively charged. The most widely used anionic surfactants are those containing carboxylate groups, such as soaps, sulfonates, and sulfate ions. In cationic surfactants, the head groups are positively charged. Some examples include amine and quaternary ammonium salts. Cationic surfactants are not used in pharmaceutical systems because of their toxicity since they adsorb readily to cell membrane structures in a nonspecific manner, leading to cell lysis (46).

As shown in Figure 5, surfactants typically orient themselves at polar/nonpolar interfaces because of the presence of discrete hydrophobic and hydrophilic regions. As the bulk concentration of surfactant in solution is increased, the surfactant molecules begin to associate into small aggregates called micelles, whereby their hydrophobic regions are shielded from aqueous contact by their hydrophilic regions. All surfactant molecules in excess of that concentration associate into micelles, while the concentration of nonassociated surfactant molecules remains nearly constant. The concentration at which such association occurs is called critical micelle concentration (CMC). Using soap as a micelle forming substance, Lawrence proposed in 1937 that poorly soluble hydrophobic molecules locate in the hydrocarbon core of the micelle, while polar molecules would associate with the polar end (47). Molecules that contain polar and nonpolar groups align themselves between the chains of the micelle with the nonpolar part directed into the central region and the polar end extending out into the hydrophilic chains (Fig. 6).

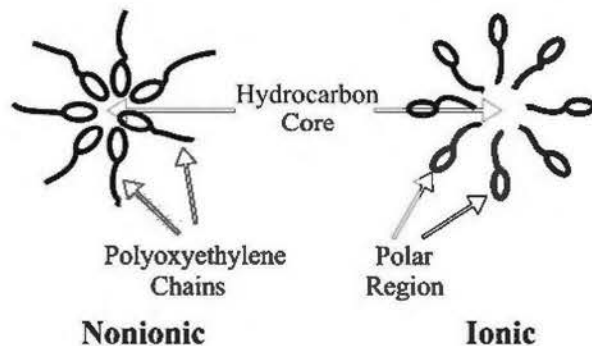


Figure 5 Illustration of spherical orientations of nonionic and ionic micelles.

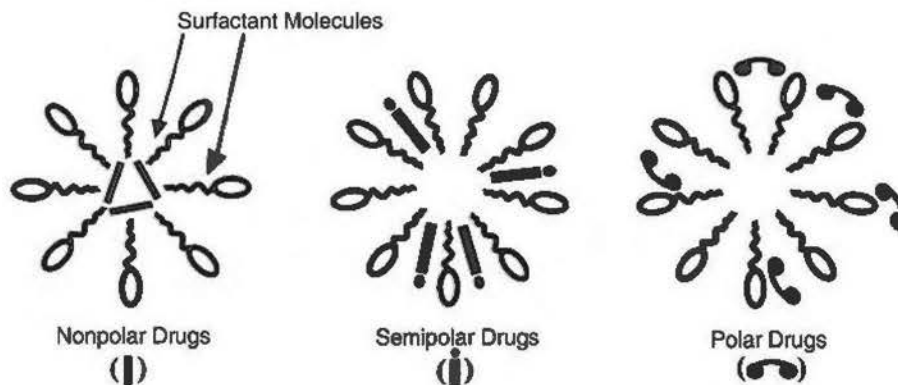


Figure 6 Schematic representation of mechanisms of micellar solubilization.

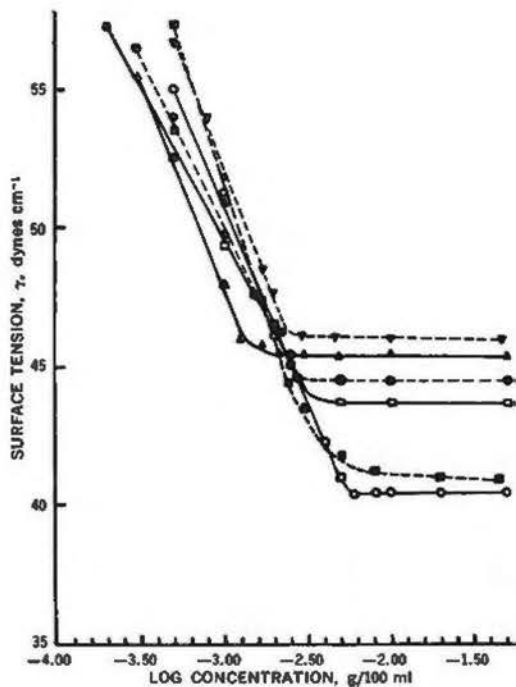
**Table 6** Effect of Surfactants on the Solubility of Furosemide

Surfactant % (w/v)	Distilled water		0.1 N hydrochloric acid	
	Total solubility (µg/mL)	Micellar solubility (µg/mL)	Total solubility (µg/mL)	Micellar solubility (µg/mL)
0	41.2		15.0	
Polysorbate 20 (C12)				
0.005	31.2		40.0	
0.05	45.0	3.7	41.1	26.1
0.5	57.0	15.7	50.0	35.0
1.0	167.0	125.7	145.0	130.0
5.0	705.0	663.7	670.0	655.0
Polysorbate 40 (C16)				
0.005	32.5		25.0	
0.05	45.0	3.7	22.5	7.5
0.5	112.5	71.2	72.5	57.5
1.0	143.7	102.4	137.5	122.5
5.0	792.5	751.2	887.0	872.0
Polysorbate 80 (C18)				
0.005	43.7	2.4	15.9	0.9
0.05	43.7	2.4	18.7	3.7
0.5	141.2	100.0	74.0	59.0
1.0	205.0	163.7	160.0	145.0
5.0	980.0	938.7	808.0	793.0

Source: From Ref. 49.

Generally, the solubilization capacity of a same amount of surfactant is high for those with lower CMC value. The solubilizing ability of nonionic surfactant toward water-insoluble drugs has been extensively studied (48). Akbuga and Gursoy (49) showed how the solubility of furosemide, a very insoluble compound commonly used as diuretic, was dramatically affected by the surfactant concentration and alkyl chain length (Table 6).

The CMC can be measured by a variety of techniques, for example, surface tension, light scattering, osmometry, all of which show a characteristic break point in the plot of the operative property as a function of concentration. Figure 7, a plot of surface tension against concentration of surfactant shows a break in the linearity of the curve, indicating the CMC (50). Many factors such as temperature, pH of the solution, electrolytes, and other ingredients affect micellization and hence solubilization (51,52). For nonionic surfactants, the CMC value decreases with increasing temperature whereas for ionic surfactants, it increases as the temperature increases (53). Since the pH can affect the equilibrium between ionized and nonionized solute species, it can have an effect on the capacity of micellar solubility as shown by Castro et al, for atenolol, nadolol, midazolam and nitrazepam (54). For ionic surfactant micelles, electrolyte addition causes a decrease in the CMC resulting in an increase in the micellar solubilization capacity (55), whereas in the case of nonionic surfactant, polysorbate 80, the solubility of furosemide increases in the presence of sodium chloride because of increased micellar packing and micelle volume (56). Other ingredients present in the formulation can also have a profound effect on the solubilizing capacity of surfactants. Surfactants may precipitate in the presence of some organic additives or micellization may be abolished if high enough concentrations of, for example, alcohols are present. Excipients such as phospholipids also affect the CMC. Many water-soluble drugs themselves are remarkably surface active: they lower the surface and interfacial tension of water, promote foaming, and associate into micelles, such as antibacterial (hydrochlorides of acridines, benzalkonium chloride, cetylpyridinium chloride) tranquilizers (hydrochlorides of reserpine and phenothiazine derivatives), local anesthetics (hydrochlorides of procaine, tetracaine, dibucaine, and lidocaine), nonnarcotic analgesic (propoxyphene hydrochloride) and narcotic analgesic (morphine sulfate and meperidine hydrochloride), antimuscarinic drugs (propantheline bromide, methantheline bromide, methixene hydrochloride), cholinergic agents (pilocarpine hydrochloride, and other



**Figure 7** Surface tension versus concentration of surfactant. Break in the curve denotes CMC. Source: From Ref. 50.

alkaloidal salts), antihistamines (pyrilamine maleate, tripeleminamine hydrochloride, chlorcyclizine hydrochloride, diphenhydramine hydrochloride), anthelmintics (lucanthone hydrochloride), and antibiotics (sodium fusidate, some penicillins, and cephalosporins) (46).

Selection of surfactant in the injectable products should be based on its safety and toxicology profile (LD50, tissue tolerance, hemolysis, etc.), solubility of the drug in the surfactant, and drug-surfactant compatibility. Since surfactants act as nonspecific solubilizers, stabilizers, emulsifiers and wetting agents, they can also cause toxicity and disrupt normal membrane structure. As mentioned earlier, only nonionic surfactants are generally used in parenterals because of their relative less destruction to biological membranes. Table 7 lists some commonly used surfactants, their properties, and examples of marketed injection products that contain surfactants for the purpose of solubility enhancement. Polysorbate 80 is

**Table 7** List of Some Surfactants in Injectable Products and Their Properties

Surfactant	Chemical name	HLB <sup>a</sup> value	CMC (% w/w)	Injection product (chemical/brand/% surfactant)
Cremophor	Polyoxyethylated castor oil	12 14	0.02	Paclitaxel/taxol/52.7 Tenoposide/vumon/55 Cyclosporine/sandimmune/65 Vitamin K /Aqua mephyton/25
Solutol HS	Polyethylene glycol 660 hydroxystearate	14 16	0.03	
Pluronic F68	Polaxomer	>24	0.1	Recombinant Growth hormone/accretropin/0.2
Polysorbates	Tween 80	15	0.0014	Amiodorone/cordarone/10 docetaxel/taxotere/100 Vitamin A palmitate/aquasol A/12
	Sodium desoxycholate	16	0.08	Amphotericin/fungizone/0.4
	Sodium dodecyl sulfate	40	0.03	Aldesleukin/proleukin/0.018

<sup>a</sup>Hydrophilic Lipophilic Balance

the most commonly used surfactant and is used in the range from fraction of percent in many products to 100% in the case of taxotere injection.

**Cyclodextrins as solubilizers** Cyclodextrins are oligomers of glucose produced by enzymatic degradation of starch. The number of  $\alpha$ -1,4-linked glucose units determine the classification into  $\alpha$ ,  $\beta$ , or  $\gamma$  cyclodextrins having six, seven, or eight glucose units, respectively (57-59). The cyclodextrins exert their solubilizing effect by forming soluble inclusion complexes in aqueous solutions. The cyclodextrins are amphiphatic (i.e., the exterior is hydrophilic due to the hydroxy groups oriented on the exterior while the interior is hydrophobic) and can form soluble, reversible inclusion complexes with water-insoluble compounds. The unsubstituted cyclodextrins are too toxic for parental use but the chemically modified cyclodextrins appear to be well tolerated when administered parenterally and have been shown to effectively enhance the solubility of several drugs including steroids and proteins (60,61). The solubility of alfaxalone, an insoluble anesthetic, was increased by 5000 times to 19 mg/mL in 20% hydroxypropyl- $\beta$ -cyclodextrin (62). Some other examples of injectables that are currently in the market which contain chemically modified cyclodextrin for the purpose of enhancement of solubility are: Aripiprazole (Abilify<sup>®</sup>) (63), ziprasidone (Geodon<sup>®</sup>) (64) and voriconazole (Vfend<sup>®</sup>) (65) containing sulfobutylether  $\beta$  cyclodextrin (SBECD), itraconazole (Sporanox<sup>®</sup>) (66) containing hydroxypropyl- $\beta$ -cyclodextrin, and others.

Having reviewed the factors that govern solubility and solubilization during the formulation development of injectable products, the next considerations are the elements of formulations.

#### Types of vehicles

**Aqueous** The vast majority of injectable products are administered as aqueous solutions because of the physiological compatibility of water with body tissues. Additionally, the high DC of water makes it possible to dissolve ionizable electrolytes, and its hydrogen-bonding potential facilitates the solution of alcohols, aldehydes, ketones, and amines. The current USP (1) has monographs for purified water, sterile purified water, WFI, sterile WFI, bacteriostatic WFI, sterile water for inhalation, and sterile water for irrigation.

WFI is the solvent of choice for making parenterals. It must be prepared fresh and be pyrogen-free. It must meet all the chemical requirements for sterile purified water and in addition the requirements for bacterial endotoxins. The tests required for WFI are generally the same among the various pharmacopeias but differences do exist with regards to limits. WFI may be prepared by either distillation or reverse osmosis but the distillation method is by far the most common and accepted method. Because of the excellent solvent properties of water, it is both difficult to purify and maintain purity. Microorganisms, dissolved gases, organic and inorganic substances, and foreign particulate matter are the most common contaminants of water.

Prior to distillation, the water used as the source for WFI is usually subjected to chlorination, carbon treatment, deionization, and, sometimes, reverse osmosis treatment (forced passage through membrane materials). After distillation, it is filtered and then stored in a chemically resistant tank (stainless steel, glass, or blocked tin) at a cold temperature around 5°C or at an elevated temperature between 65°C and 85°C to inhibit microbial growth and prevent pyrogen formation. Generally, the hot water is continually circulated in the manufacturing areas during storage and usually filtered again prior to use. Sterile WFI and Bacteriostatic WFI are permitted to contain higher levels of solids than WFI because of the possible leaching of glass container constituents into the water during sterilization and storage. Bacteriostatic WFI, which generally contain 0.9% (9 mg/mL) of benzyl alcohol as a bacteriostatic preservative, should not be sold in containers larger than 30 mL to prevent injection of unacceptably large amounts of bacteriostatic agents (such as phenol and thimerosal).

**Other water-miscible cosolvents** These have been discussed earlier.

**Nonaqueous vehicles** Drugs that are insoluble in aqueous systems are often incorporated in metabolizable oils. Steroids, hormones, and vitamins are incorporated in vegetable oils such as peanut, sesame, corn, olive, and cottonseed. Oil injections are only administered intramuscularly. There are strict specifications for the vegetable oils used in manufacturing

**Table 8** Official Injections Containing Oils as Vehicles

USP (1)	Oil commonly used
Desoxycorticosterone acetate	Sesame
Diethylstilbestrol	Sesame, cottonseed
Dimercaprol (suspension)	Peanut
Estradiol cypionate	Cottonseed
Estradiol valerate	Sesame
Estrone	Sesame
Ethiodized iodine	Poppyseed
Fluphenazine decanoate	Sesame
Fluphenazine enanthate	Sesame
Hydroxyprogesterone caproate	Sesame
Menadione	Sesame
Nandrolone decanoate	Sesame
Nandrolone phenpropionate	Sesame
Penicillin G procaine (combinations)	Vegetable
Propylidone (suspension)	Peanut
Testosterone cypionate	Cottonseed
Testosterone enanthate	Sesame
Testosterone propionate	Sesame

intramuscular injections. Storage of these preparations is important if stability is to be maintained. For example, they should not be subjected to conditions above room temperature for extended periods of time. Although the oils used for injections are of vegetable origin, federal regulations require that the specific oil be listed on the label of a product, because some patients have exhibited allergic responses to certain vegetable oils.

Sesame oil is the preferred oil for most of the compendial injections formulated with oil. It is the most stable of the vegetable oils (except to light), because it contains natural antioxidants. Sesame oil has also been used to obtain slow release of fluphenazine esters given intramuscularly (67). Excessive unsaturation of oil can produce tissue irritation. In recent years, the use of injections in oil has diminished somewhat in preference to aqueous suspensions, which generally have less irritating and sensitizing properties. Benzyl benzoate may be used to enhance steroid solubility in oils if desired. Table 8 lists the oil injections official in the current USP (1).

#### *Added Substances*

Added substances such as buffers, antioxidants, antimicrobial preservatives, tonicity adjusting agents, bulking agents, chelating agents, solubilizing agents, and surfactants must frequently be incorporated into parenteral formulas in order to provide safe, efficacious, and elegant parenteral dosage forms. However, any such additive may also produce negative effects such as loss of drug solubility, activity, and/or stability. Any additive to a formulation must be justified by a clear purpose and function. No coloring agent may be added, solely for the purpose of coloring the finished preparation, intended for parenteral administration (1). The reader is encouraged to refer to a number of publications that provide comprehensive listing of formulation components used in all marketed injectable products (1,68-74). Hospital pharmacists who are involved in IV additive programs should be aware of the types of additives present in products that are being combined. Commonly used parenteral additives and their usual concentrations are listed in Table 9.

Pharmacopeias often specify the type and amount of additive substances that may be included in injectable products. These requirements often vary from compendia to compendia, so it is important to refer to the specific pharmacopeia that applies to the product in question. USP (1) specifies following maximum limits in preparations for injection that are administered in a volume exceeding 5 mL: for agents containing mercury and the cationic surface-active compounds, 0.01%; for chlorobutanol, cresol, phenol, and similar types of substances, 0.5%; and for sulfur dioxide, or an equivalent amount of the sulfite, bisulfite, or metabisulfite of

**Table 9** Commonly Used Parenteral Additives and Their Usual Concentration

Added substance	Usual concentrations (%)
<b>Antibacterial preservatives</b>	
Benzalkonium chloride	0.01
Benzethonium chloride	0.01
Benzyl alcohol	1 2
Chlorobutanol	0.25 0.5
Chlorocresol	0.1 0.3
Metacresol	0.1 0.3
Phenol	0.5
Phenylmercuric nitrate and acetate	0.002
Methyl p hydroxybenzoate	0.18
Propyl p hydroxybenzoate	0.02
Butyl p hydroxybenzoate	0.015
Thimerosal	0.01
<b>Antioxidants</b>	
Acetone sodium bisulfite	0.2
Ascorbic acid	0.01
Ascorbic acid esters	0.015
Butylhydroxyanisole (BHA)	0.02
Butylhydroxytoluene (BHT)	0.02
Cysteine	0.5
Nordihydroguaiaretic acid (NDGA)	0.01
Monothioglycerol	0.5
Sodium bisulfite	0.15
Sodium metabisulfite	0.2
Tocopherols	0.5
Glutathione	0.1
<b>Chelating agent</b>	
Ethylenediaminetetraacetic acid salts	0.01 0.075
DTPA	0.01 0.075
<b>Buffers</b>	
Acetic acid and a salt, pH 3.5 5.7	1 2
Citric acid and a salt, pH 2.5 6	1 5
Glutamic acid, pH 8.2 10.2	1 2
Phosphoric acid salts, pH 6 8.2	0.8 2
<b>Tonicity adjustment</b>	
Dextrose	4 5.5
Sodium chloride	0.5 0.9
Mannitol	4 5

potassium or sodium, 0.2%. Ethylenediaminetetraacetic acid derivatives and salts are sometimes used to complex and thereby inactivate trace metals that may catalyze oxidative degradation of drugs. The properties and function of these added substances will be reviewed next, except solubilizing agents and surfactant, which have been reviewed earlier.

**Buffers.** Maintenance of appropriate pH of the formulation is essential for proper solubility and stability. Changes in the pH of a formulation may occur during storage because of degradation reactions within the product, interaction with container components (i.e., glass or rubber), and absorption or evolution of gases and vapors. Buffers are added to many products to resist a change in pH. Excellent reviews on pH control within pharmaceutical systems by Flynn (75) and Nema et al (76) are recommended to the reader. A suitable buffer system should have an adequate buffer capacity to maintain the pH of the product at a stable value during storage, while permitting the body fluids to adjust the pH easily to that of the blood following administration. Therefore, the ideal pH to select would be 7.4, the pH of the blood. Extreme deviation from this pH can cause complications. Tissue necrosis often occurs above pH 9, while extreme pain and phlebitis are experienced below pH 3. The acceptable range for IV injections is 3 to 9 because blood itself is an excellent buffer and can very quickly neutralize the



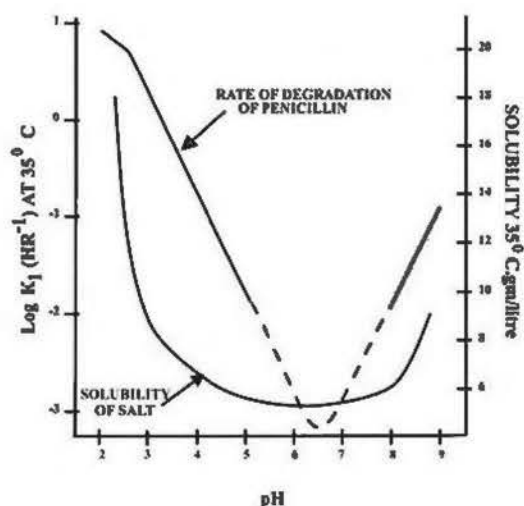


Figure 8 Solubility/stability pH profile of procaine penicillin. Source: From Ref. 77.

pH outside of 7.4. Parenterals administered by other routes are generally adjusted to a pH between 4 and 8.

A suitable buffer system can be selected from knowledge of a solubility/stability pH profile of the drug in solution. A typical pH profile of both solubility and stability is shown in Figure 8 for procaine penicillin G (77). By following the degradation over a given pH range and plotting the rate constants versus pH, the pH of maximum stability (pH 6.6) can be determined. In the case of procaine penicillin G, the solubility is lowest between the pH 6 and 7, which is desirable since the product is formulated as a suspension. Once the desired pH is determined, a buffer system that provides sufficient buffer capacity can be selected. The buffer capacity,  $\beta$ , is an indication of the resistance to change in pH upon the addition of either basic or acid substances and can be represented by the following expression:

$$\beta = \frac{dB}{d\text{pH}} = 2.303C \frac{K_a H^+}{(K_a + H^+)} \quad (11)$$

where

$dB$  = change in concentration of base or acid,  
 $d\text{pH}$  = change in pH,  
 $C$  = molar concentration of buffer system, and  
 $K_a$  = dissociation constant of the buffer.

A hypothetical plot of  $\beta$  versus  $\text{pH} - \text{p}K_a$  is illustrated in Figure 9 for a monobasic acid. A maximum value at zero indicates that the greatest buffer capacity occurs at a pH equal to the  $\text{p}K_a$  of the buffer system and further suggests that a buffer system with a  $\text{p}K_a$  within  $\pm 1.0$  unit of the desired pH should be selected.

Buffer systems for parenterals generally consist of either a weak base and the salt of a weak base or a weak acid and the salt of a weak acid. Figure 10 shows the effective range of typical pharmaceutical buffers. The distance indicated by the arrows represents the effective buffer range for each system and the dashed lines represent the  $\text{p}K_a$  for the system. Commonly used buffers are phosphates, citrate, acetate, and glutamates.

The Henderson-Hasselbach relationship is used to calculate the quantities of buffer species required to provide a desired pH.

$$\text{pH} = \text{p}K_a + \log \frac{C_{\text{salt}}}{C_{\text{acid}}} \quad (12)$$

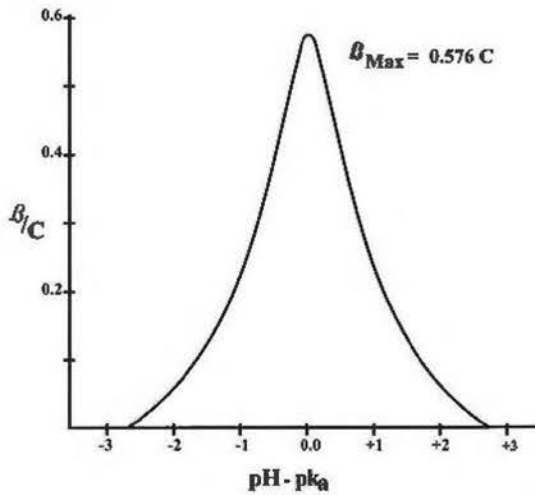


Figure 9 Theoretical buffer capacity curves of a monobasic acid.

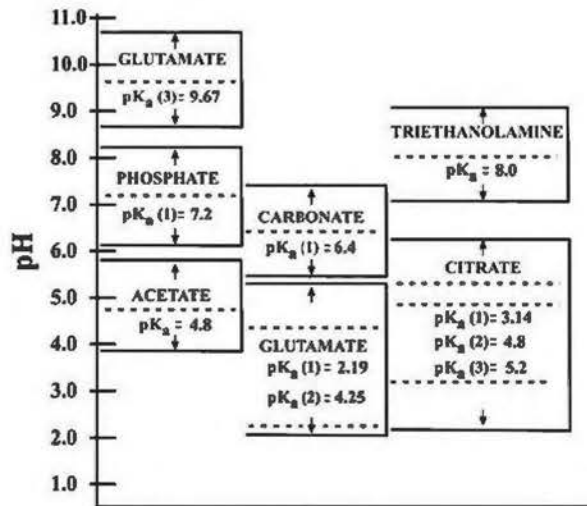


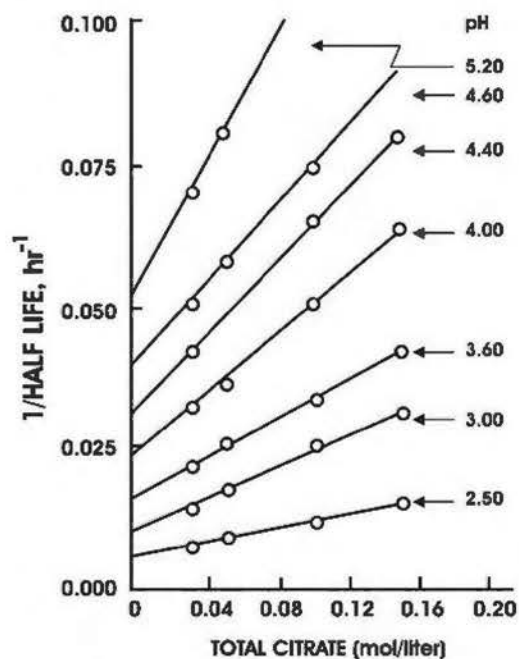
Figure 10 Effective range of pharmaceutical buffers, indicated by the arrows. The dashed line represents the pKa value.

Where  $C_{\text{salt}}$  and  $C_{\text{acid}}$  are the molar concentrations of the salt form and the acid form, respectively. As shown from the following calculation, an acetate buffer system ( $pK_a = 4.8$ ) consisting of 0.1 M acetic acid and 0.05 M sodium acetate would result in a pH of 4.5.

$$pH = 4.8 + \log \frac{0.05}{0.1} = 4.8 - 0.3 = 4.5$$

Although buffers assure the stability of pH of solution, the buffer system itself can affect other properties such as reaction kinetics and solubility aspects. Buffers can act as general acid or general base catalysts and cause degradation of some drug substances. Such a mechanism occurs with a number of amine and amine derivative drugs in systems containing polycarboxylic acids (e.g., citric, tartaric, and succinic). In one such case, as shown in Figure 11, the degradation of vitamin B<sub>1</sub> increases with increase in citrate buffer concentration (78).

The ionic strength contributions of the buffer system can also affect both isotonicity and stability. For example, if adjustment of pH is made with sodium hydroxide, say of a solution



**Figure 11** Effect of citrate buffer concentration on thiamine hydrolysis (vitamin B1) at 96.4°C at constant ionic strength and at different pH values. Source: From Ref. 78.

containing monosodium phosphate, the effect of the generation of disodium salt on isotonicity and the effect of  $\text{HPO}_4^{-2}$  must be taken into account (79,80).

**Antioxidants.** Many drugs in solution are subject to oxidative degradation. Such reactions are mediated either by free radicals or by molecular oxygen and often involve the addition of oxygen or the removal of hydrogen. For products in which oxygen is directly involved in the degradation, protection can be afforded by displacing oxygen (air) from the system. This is accomplished by bubbling nitrogen, argon, or carbon dioxide through the solution prior to filling and sealing in the final container. Oxidative decomposition is catalyzed by metal, hydrogen, and hydroxyl ions. Drugs possessing a favorable oxidation potential will be especially vulnerable to oxidation. For example, a great number of drugs are formulated in the reduced form (e.g., epinephrine, morphine, ascorbic acid, menadione, etc.) and are easily oxidized. Oxidation can be minimized by increasing the oxidation potential of the drug. As illustrated in Figure 12 (81), lowering the pH of the solution will increase the oxidation potential. This occurs because according to a simplified version of the Nernst equation:

$$E = E^0 + \frac{RT}{2} \log \frac{[\text{H}^+] \cdot [\text{Ox}]}{[\text{Rd}]} \quad (13)$$

an increase in hydrogen ion concentration causes an increase in the actual oxidation potential,  $E$ . In this equation  $E^0$  is the standard oxidation potential,  $R$  the gas constant,  $T$  the absolute temperature, and constant 2 represents the number of electrons taking part in the oxidation-reduction reaction.

Agents that have a lower oxidation potential than the drug in question, and thus can be preferentially oxidized, are called antioxidants. Such agents are added to parenteral solutions either alone or in combination with a chelating agent or other antioxidant and function in at least two ways: (i) by being preferentially oxidized and thereby gradually consumed or (ii) by blocking an oxidative chain reaction in which they are not usually consumed.

Morphine in aqueous solution undergoes a pH-dependent oxidative degradation. The rate is slow and constant between pH 2 and 5, where morphine exists in the protonated form as

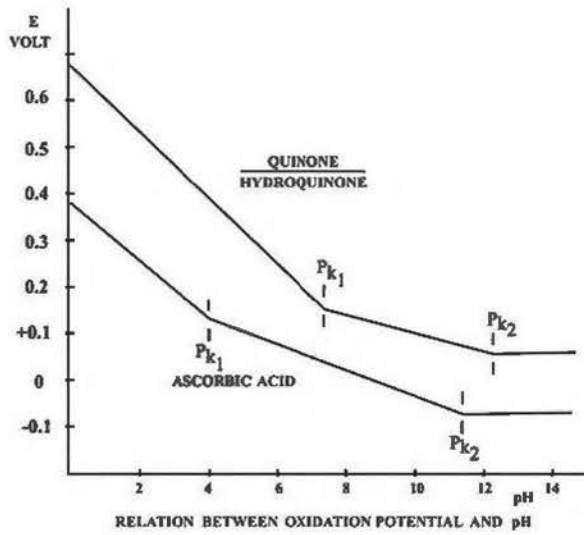


Figure 12 Relationship between oxidation potential and pH. Source: From Ref. 81.

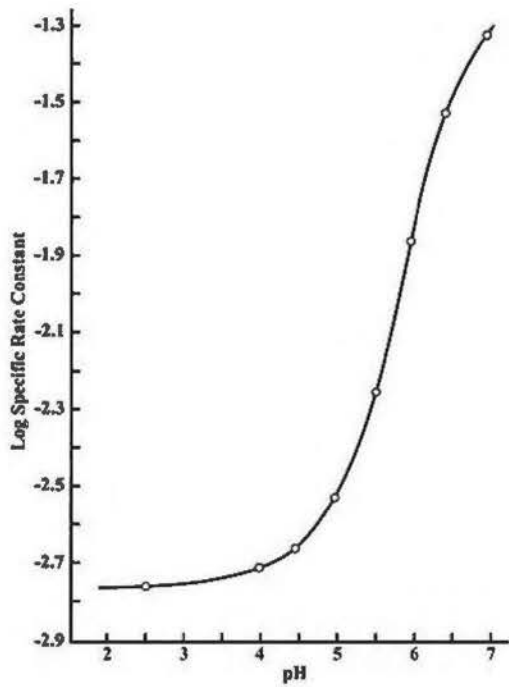


Figure 13 Reaction rate constant for the first order oxidative degradation of morphine at 95°C as a function of pH. Source: From Ref. 82.

shown in Figure 13. However, above pH 5, the oxidation increases with increase in pH (82). Therefore, morphine can be stabilized by lowering the pH or by adding an antioxidant such as ascorbic acid which will be preferentially and reversibly oxidized between pH 5 and 7. Ascorbic acid, in turn, can act as an antioxidant for hydroquinone because it has a lower oxidation potential and will be preferentially oxidized. Table 10 lists some standard oxidation

**Table 10** Some Commonly Used Antioxidants and Their Oxidation Potentials

Substance	$E^{\circ}$ (V)	pH	Temperature ( $^{\circ}$ C)
Riboflavin	+0.208	7.0	30
Dithiothreitol	+0.053	7.0	30
Sodium thiosulfate	+0.050	7.0	30
Thiourea	+0.029	7.0	30
Ascorbic acid <sup>a</sup>	+0.003	7.0	25
	0.115	5.2	30
	0.136	4.58	30
Methylene blue	0.011	7.0	30
Sodium metabisulfite <sup>a</sup>	0.114	7.0	25
Sodium bisulfite <sup>a</sup>	0.117	7.0	25
Propyl gallate <sup>a</sup>	0.199	7.0	25
Acetylcysteine <sup>a</sup>	0.293	7.0	25
Vitamin K	0.363		20
Epinephrine	0.380	7.0	30
Hydroquinone	0.673		
Resorcinol	1.043		
Phenol <sup>a</sup>	1.098		

<sup>a</sup>Common in parenteral products

potentials. Salts of sulfur dioxide, including bisulfite, metabisulfite, and sulfite are the most common antioxidants in aqueous solutions. Irrespective of which salt is added to the solution, the antioxidant moiety depends on the final concentration of the compound and the final pH of the formulation (83). The metabisulfite is used at low pH values (84). Some drugs can be inactivated by bisulfites. For example, in the presence of bisulfite, epinephrine forms addition product as epinephrine sulfonate, which is inactive (85). Ortho or para-hydroxybenzyl alcohol derivatives such as parabens react in a similar manner.

While undergoing oxidation reactions, the sulfites are converted to sulfates. Since small amounts (picograms) of barium or calcium can be extracted even from type I glass, an insoluble sulfate can form in the solution (86). Therefore, additional care must be exercised to visibly inspect preparations containing sulfite antioxidants or sulfate drugs for the presence of fine particles which will appear, upon gently shaking, as a swirl originating from the bottom of the container. Sulfite levels are determined by the reactivity of the drug, the type of container (glass seal vs. rubber stopper), single or multiple-dose use, container headspace, and the expiration dating period to be employed.

Another antioxidant, Glutathione, an electron donor, stabilized the photooxidation of menadione, a synthetic analogue of Vitamin K by a charge transfer complex formation (87), thereby blocking the light-catalyzed oxidative chain reaction.

Often a single antioxidant may not be sufficient to completely protect the product. Certain compounds have been found to act as synergists, increasing the effectiveness of antioxidants, particularly those that block oxidative reactions, e.g., ascorbic acid and citric acid. Frequently, chelating agents such as ethylenediaminetetraacetic acid (EDTA) salts are used because these salts form complexes with trace amounts of heavy metals which otherwise would catalyze oxidative reactions. While incorporating such antioxidants, the formulator must be aware of their potential side effects. Although, very widely used, sulfites are associated with several effects upon parenteral administration, including flushing, pruritus, urticaria, dyspnea, and bronchospasm (88).

In practice, several approaches can be utilized by the formulator to protect the product from oxidative instability, such as purging the solution and headspace with inert gas to exclude oxygen, lowering the pH, and addition of an antioxidant. One must ensure use of high purity excipients since trace impurities, namely peroxides and metals, carried into a formulation through ingoing components, may also have a catalyzing effect on the auto-oxidation pathway. Well-protected, properly sealed packages that provide an acceptable headspace-to-product ratio can also provide some robustness to the product, thus making it

**Table 11** List of Commonly Used Antibacterial Preservatives and Their MICs

Agent	MIC <sup>a</sup> range	Amount most often used (%)
Benzalkonium chloride	0.005 0.03	0.01
Benzethonium chloride	0.005 0.03	0.01
Benzyl alcohol	1.0 10.0	1.0
Chlorobutanol	0.2 0.8	0.5
Chlorocresol	0.1 0.3	0.1 0.25
Cresol	0.1 0.6	0.3
Parabens (methyl, ethyl, propyl, butyl esters)	0.05 0.25 methyl 0.005 0.03 others	0.18 0.02
Phenol	0.1 0.8	0.5
Phenylmercuric nitrate	0.001 0.05	0.002
Thimerosal	0.005 0.03	0.01

<sup>a</sup>Affected by product pH, ionic strength, storage temperature, packaging materials, etc.  
Abbreviation: MIC, minimum inhibitory concentration.

less sensitive to oxidation (89). Process control is required for assurance that every container is deaerated adequately and uniformly.

**Antimicrobial preservatives.** Agents with antimicrobial activity must be added to preparations packaged in multiple-dose containers unless prohibited by compendial monograph or unless the drug itself is bacteriostatic, for example, methohexital sodium for injection and most of the cytotoxic anticancer products. A partial list of antimicrobial preservatives used in pharmaceutical systems along with their minimum inhibitory concentrations (MICs), is presented in Table 11.

An excellent review is published by Meyer et al (90) that provides a comprehensive summary of antimicrobial preservatives that are commonly used in licensed parenteral products to date. It was noted that the most commonly used eight antimicrobial preservatives in all parenteral products at the present are: phenol, benzyl alcohol, chlorobutanol, m-cresol, methylparaben, phenoxyethanol, propylparaben, and thimerosal with the three most commonly used preservatives in small molecule injection products are phenol, benzyl alcohol, and parabens.

Phenol is a bacteriostatic when present in 1% w/v solution and has activity against mycobacteria, fungi, and viruses (91). The solubility of phenol in water is 1 in 15 (w/w) at 20 °C. Aqueous solutions of phenol are stable, can be sterilized by dry heat or autoclaving, and should be maintained in containers that are protected from light. Phenol is incompatible with albumin and gelatin, which will result in precipitates possibly due to phenol-induced denaturation of these molecules. There is a low likelihood of adverse reactions from phenol in parenteral products due to the low concentrations used in these products.

Benzyl alcohol is an aromatic primary alcohol and is effective against most Gram-positive bacteria, yeast, and mold, but is less effective against gram-negative bacteria. Its solubility in water is 1 in 25 (w/w) at 25 °C. The optimum antimicrobial activity occurs at pH less than 5 and is less active above pH 8.3. It may be stored in glass or metal containers or in polypropylene containers coated with Teflon or other inert fluorinated polymers (92).

Parabens are benzoic acid esters and have a broad spectrum of antimicrobial activity at a pH range of 4–8, but are more effective against yeasts and molds when compared with bacteria. Antimicrobial activity is normally enhanced when combinations of parabens are used with excipients such as propylene glycol, phenylethyl alcohol, and edetic acid (93). Aqueous solutions of parabens are stable at a pH range of 3 to 6, but degrade by hydrolysis at pH greater than 8. The solubility of methylparaben and propylparaben in water is 1 in 400 (w/w) at 25 °C, and 1 in 2500 at 20 °C, respectively (92). Because of inherent low solubilities, sodium salts are frequently utilized in the final dosage forms.

Antimicrobial agents are specifically excluded in the large-volume injections that are used to provide fluids, nutrients, or electrolytes, such as dextrose and sodium chloride injection, dextrose injection, ringer's injection, lactated ringer's injection, and sodium chloride

injection. Bacteriostatic agents may be added to dextrose and sodium chloride injection when it is labeled for use as a sclerosing agent, because the amount of injection used for such purposes is small, and the quantity of antibacterial present would not be harmful to the patient.

The two main considerations while selecting an antimicrobial preservative in the injection products are their compatibility and effectiveness.

Many papers have been published describing the incompatibilities or binding of preservatives with surfactants, pharmaceuticals, and rubber closures (94-99).

Antimicrobial activity of preservative parabens, which was due to the concentration of the free form, was shown to be significantly reduced in the presence of polysorbate because of binding (96). Rubber closures and rubber extractives have also been found to influence significantly preservative loss from solution and antimicrobial activity, respectively. Lachman and coworkers (98,99) studied the interaction of preservatives with various types of rubber and found significant losses of a number of preservatives (i.e., chlorobutanol, chlorophenylethyl alcohol, methylparaben, and benzyl alcohol) with natural and neoprene rubber whereas the loss was minimal in the presence of butyl rubber.

The effectiveness of antimicrobial agents can be determined using a test described in compendia as "antimicrobial effectiveness testing." The test typically consists of inoculating  $10^5$ – $10^6$  CFU/mL microorganisms (e.g., bacteria and fungi) per container at time zero, and evaluating the log reduction over time. The criterion used for passing this test is as follows:

Bacteria: Not less than 1.0 log reduction from the initial calculated count at 7 days, not less than 3.0 log reduction from the initial calculated count at 14 days, and no increase from the 14 days' count at 28 days.

Yeasts and molds: No increase from the initial calculated count at 7, 14, and 28 days.

It is recommended that this test should be performed with the formulation throughout and near the end of the expiration date to ensure that adequate levels of preservative are still available.

While the need for an antimicrobial is clearly obvious, there have been recent concerns and evidence of irritation from these agents. Therefore, it is essential to keep the concentration as low as possible, recognizing that these agents act by killing living cells and do not differentiate the good cells from the bad ones.

**Tonicity.** To minimize tissue damage and irritation, reduce hemolysis of blood cells, and prevent electrolyte imbalance upon administration of small-volume parenterals, the product should be isotonic, or nearly so. Isotonic solutions exert the same osmotic pressure as blood plasma. Solutions may also exert less (hypotonic) or more (hypertonic) osmotic pressure than plasma. Red blood cells (RBCs; erythrocytes) when introduced into hypotonic solution will swell and often burst (hemolysis) because of diffusion of water into the cell. If the cells are placed into hypertonic solutions, they may lose water and shrink (crenation). In isotonic solutions (e.g., 0.9% sodium chloride) the cells maintain their "tone" and the solution is isotonic with human erythrocytes. Isotonicity of formulation is not always feasible as a result of the high concentrations of drug utilized, the low volumes required for some injections, the wide variety of dose regimens and methods of administration, and product stability considerations. Historically, there has been concern over the osmolarity or tonicity of IV infusion fluids because of the large amounts of solution administered to hospitalized patients, but in the last few years there has also been interest in the osmolarity of other parental dosage forms.

Sodium or potassium chloride and dextrose are commonly added to adjust hypotonic solutions. There are several methods available to calculate tonicity (100). The sodium chloride equivalent method is the most convenient. The sodium chloride equivalent of a substance can be determined from its ability to lower the freezing point of water. A 1% sodium chloride solution has a freezing point of  $-0.58^\circ\text{C}$  and is assigned a sodium chloride equivalent, *E*, of 1.00. The freezing point of blood (serum) is  $-0.58^\circ\text{C}$ , the same as a 0.9% w/v solution of sodium chloride. If a 1% solution of a substance has a freezing point of  $-0.058^\circ\text{C}$ , the *E* value will be 0.1. Therefore, 1.0 g of the substance will be equivalent to 0.1 g of NaCl.

**Table 12** Sodium Chloride Equivalents and Freezing Point Depression for 1% Solutions

Agent	Sodium chloride equivalent	Freezing point depression (°C)
Atropine sulfate	0.13	0.075
Barbital sodium	0.30	0.171
Benzyl alcohol	0.17	0.09
Boric acid	0.50	0.288
Calcium chloride	0.51	0.298
Calcium disodium edetate	0.21	0.120
Calcium gluconate	0.16	0.191
Chlorobutanol	0.24	0.14
Citric acid	0.18	0.10
Codeine phosphate	0.14	0.080
Dextrose	0.16	0.091
Dimethyl sulfoxide	0.42	0.245
Edetate disodium	0.23	0.132
Ephedrine HCl	0.30	0.165
Isoproterenol sulfate	0.14	0.078
Mannitol	0.18	0.1
Penicillin G potassium	0.18	0.102
Phenol	0.35	0.20
Pilocarpine nitrate	0.23	0.132
Polyethylene glycol 300	0.12	0.069
Polyethylene glycol 400	0.08	0.047
Sodium bisulfite	0.61	0.35
Sodium cephalothin	0.17	0.095
Sodium chloride	1.00	0.576
Sodium citrate	0.31	0.178
Sodium phosphate, dibasic	0.42	0.24
Sodium sulfate, anhyd	0.58	0.34
Sucrose	0.08	0.047
Urea	0.59	0.34

To make 100 mL of a 1% solution of the substance isotonic, 0.8 g of sodium chloride must be added. A partial list of sodium chloride equivalents of variety of parenteral additives is shown in Table 12.

In the absence of a sodium chloride equivalent the  $L_{iso}$  method can be used as shown by Goyan, et al, in 1944 (101). The  $L_{iso}$  is the value at which a specific compound type will be isotonic with blood. It is related to sodium chloride equivalent in the following manner:

$$E = 17 \frac{L_{iso}}{M} \quad (14)$$

where M is the molecular weight of the substance. Table 13 shows some  $L_{iso}$  values for various types of compounds. The calculation of tonicity is illustrated by the following example.

It is desired to make a 2 g/100 mL solution of sodium cephalothin isotonic using sodium chloride. Sodium cephalothin has a molecular weight of 238.

**Table 13**  $L_{iso}$  Values for Various Types of Additives in Parenteral Formulations

Compound type	$L_{iso}$	Example
Nonelectrolyte	1.9	Sucrose
Weak electrolyte	2.0	Phenobarbital
Divalent electrolyte	2.0	Zinc sulfate
Univalent electrolyte	3.4	Sodium chloride
Univalent electrolyte	4.3	Sodium sulfate
Diunivalent electrolyte	4.8	Calcium chloride
Univalent electrolyte	5.2	Sodium phosphate
Triunivalent electrolyte	6.0	Aluminum chloride



**Table 14** Comparison of Measured Osmolality Values with Those Calculated from Sodium Chloride Equivalents

Solution (g/100 mL)	Measured osmolality mean mOsm $\pm$ SD	Sodium chloride equivalent method	
		Osmolality	Percent of measure
Dextrose			
5.0	262 $\pm$ 5.9	249	95.0
10.0	547 $\pm$ 6.2	499	91.2
20.0	1176 $\pm$ 14.9	998	84.9
Alanine glycine			
1.0	246 $\pm$ 0.5	256	104
2.0	480 $\pm$ 1.7	512	107
5.0	1245 $\pm$ 10.8	1281	103
0.2 NaCl in 5% dextrose	311 $\pm$ 5.85	312	100
0.45% NaCl in 5% dextrose	385 $\pm$ 5.48	390	98.7
Ringer's solution, USP	294 $\pm$ 4.98	281	95.6
Lactated ringer's, USP	264 $\pm$ 3.23	248	93.9
Travasol 5.5%	554 $\pm$ 11.4	596	107.6
67% travasol (5.5%) 33% dextrose (50%)	1330 $\pm$ 29.6	1323	91.9

As shown in Table 13 the  $L_{iso}$  for univalent electrolytes has a calculated value of 3.4. Therefore,

$$E = 17x \frac{3.4}{238} = \frac{57.8}{238} = 0.24g \text{ eq.}$$

Since 2 g of drug is used in the 100 mL of fluid,  $2 \times 0.24 = 0.48$  g eq. is contributed by sodium cephalothin toward the 0.90 g of sodium chloride needed for isotonicity.

Hence  $0.90 \text{ g} - 0.48 \text{ g} = 0.42$  g of sodium chloride must be added to 2 g of sodium cephalothin in 100 mL to achieve isotonicity of the resulting solution. The sodium chloride equivalent method was used for determining the osmolarity of a number of infusion solutions and compared with measured values. As shown in Table 14, there is good agreement between measured and calculated values until the concentrations become very high.

Isoosmosity, determined by physical methods, should be distinguished from isotonicity, determined by biological methods (i.e., the hematocrit method with human erythrocytes). This distinction is necessary because of the variable diffusibility of different medicinal substances across the cell membrane, which does not always behave as a truly semi-permeable membrane. Solutions that are theoretically isoosmotic with the cells may cause hemolysis because solutes diffuse through the cell membrane. For example, a 1.8% solution of urea has the same osmotic pressure as 0.9% sodium chloride, but the urea solution produces hemolysis, because urea permeates the cell membrane. If a solution is hypertonic, not much can be done with the formulation unless it can be diluted with water prior to administration. Administration of a hypertonic solution should be done slowly to permit dilution by the blood. In some cases, where injection of such solutions produces pain, as in an intramuscular injection, a local anesthetic may be added. The effect of isotonicity on reducing pain on injection is somewhat vague, although it may at least reduce tissue irritation.

#### *Special Types of Parenterals*

**Suspensions.** A parenteral suspension is a dispersed, multiphased, heterogeneous system of insoluble solid particles intended principally for intramuscular and subcutaneous injection.

Suspension formulation is desired when the drug is too insoluble or unstable to be formulated as a solution, as well as when there is a need to retard or control the release of drug from a suspension. The desirable parenteral suspension is sterile, stable, resuspendable, syringeable, injectable, and isotonic/nonirritating. Because a delicate balance of variables is required to formulate a suitable product, a suspension is one of the most difficult parenteral

forms to prepare. Such a product must not cake during shipping and storage, and should be easy to suspend and inject through 18- to 21-gauge needle throughout its shelf life.

To achieve these goals, it is necessary to control the crystallization, particle size reduction (micronization), and sterilization of the drug substance, as well as the processes involved in wetting of the drug with surfactants, aseptic dispersion and milling, and final filling into containers. Uniform distribution of the drug is required to ensure that an adequate dose is administered to the patient. Parenteral suspensions exhibit instability in ways not applicable to solutions and dry solids. This is due to the problem of crystal growth, caking, and product-package interactions.

Injectable suspensions may be made with either vegetable oils or aqueous vehicles. Many contain low concentrations of solids (5% or less) but a few, such as procaine penicillin G, may contain up to 58% w/v solids. Therefore, properties such as resuspendibility, zeta potential, rheology, and particle size distribution become important, and often need to be monitored as a part of a stability program for these products. When particles interact to form clumps or aggregates, the process is termed flocculation or agglomeration. The process of dispersing these aggregates into individual particles is called deflocculation. The size of individual particles may also change because of temperature fluctuation during storage and/or polymorphic changes. For example, if the solubility of a drug is very temperature dependent, individual crystals can dissolve or grow in size depending on the circumstances encountered. If the rate of absorption or injectability of the drug depends on the particle size distribution of the dispersed insoluble drug, the intended performance of the product may be altered.

The requirements for, limitations of, and difference between the design of injectable suspensions and other suspensions have been summarized by several authors (102,103). The requirements and limitations relate to (i) microbiological purity, (ii) ingredients allowed, and (iii) mechanical flow properties. The microbiological purity requirements, like all parenterals, involve sterility and freedom from pyrogens.

There are 38 official parenteral suspensions in the current USP (1). The wide variety of injectable suspensions can be illustrated with the following examples. Sterile Ampicillin for suspension, USP, represents a powder to which an aqueous diluent is added to make an injectable suspension. Sterile aurothioglucose suspension, USP, is an example of a ready-to-use suspension in vegetable oil. Aqueous ready-to-use suspensions include betamethasone acetate suspension, USP, and insulin zinc suspension, USP.

As shown in Table 15, a formula for an injectable suspension might consist of the active ingredient suspended in an aqueous vehicle containing an antimicrobial agent, a surfactant for wetting and preventing crystal growth (by reducing free surface energy), a dispersing or suspending agent, antioxidant, and perhaps a buffer or salt, etc. Table 16 lists materials commonly used to formulate parenteral suspensions.

Two basic methods are used to prepare parenteral suspensions: (i) sterile vehicle and powder are combined aseptically or (ii) sterile solutions are combined and the crystals are formed in situ. In the first method, an aqueous vehicle containing the water-soluble components are heat sterilized, when possible; or filtered through a 0.22  $\mu\text{m}$  sterilizing membrane filter into a presterilized mixing/filling tank. The sterile drug powder is gradually added to the sterile solution, aseptically, while mixing. The sterile drug powder, in turn, is obtained by aseptically filtering a solution of the drug through a sterilizing membrane into a

**Table 15** Examples of Injectable Suspension Formulations in the Market

Active/Brand/Conc.	Dexamethazone/ Decadron <sup>®</sup> (8 mg/mL)	Medroxyprogesterone Acetate/Depo Provera <sup>®</sup> (100 and 400 mg/mL)	Triamcinolone Acetonide/Kenalog <sup>®</sup> (10 and 40 mg/mL)
Surfactant	Polysorbate 80	Polysorbate 80	Polysorbate 80
Suspending agent	Sodium CMC	PEG 3350	Sodium CMC
Antimicrobial agent	Benzyl alcohol	Parabens	Benzyl alcohol
Antioxidant	Sodium bisulfite		
Others	Disodium edetate, sodium chloride, creatinine	Sodium chloride	Sodium chloride

**Table 16** Partial List of Ingredients Used in Aqueous Parenteral Suspensions

---

Suspending agents
Aluminum monostearate
Gelatin (nonantigenic)
Mannitol
Povidone
Sodium carboxymethylcellulose
Sorbitol
Surfactants
Lecithin (soybean)
Polyoxyethylene polyoxypropylene ethers
Polyoxyethylene sorbitan monolaurate
Polysorbate 80
Silicone antifoam
Sorbitan trioleate
Solubilizing agents
Polyethylene glycol 300
Propylene glycol
pH adjustment
Citric acid
Sodium citrate

---

sterile vessel into which a presterilized solution of antisolvent is introduced causing the drug to crystallize. The crystals or powder are separated aseptically by filtration or centrifugation, washed, dried, and sized through milling. After all tests have been completed on the bulk material, it is aseptically filled.

In the second method, the vehicle is prepared and sterilized by filtration. The drug is dissolved separately in a nonaqueous solvent and sterilized by filtration. The sterile drug solution is aseptically added to the sterile vehicle, causing the drug to crystallize. The resulting suspension is then diluted with sterile vehicle, mixed, the crystals are allowed to settle, and the supernatant solution siphoned off. The suspension is then brought to volume and filled in the normal manner. In few cases, the filled vials may be subjected to terminal sterilization if chemical properties and particle size characteristics remain unchanged post sterilization.

Rheologically, an injectable suspension can present some formidable challenges. While a suspension can usually be formulated so that it can be filled, shipped, and injected, it is frequently difficult to formulate a product in which these three qualities remain relatively unchanged throughout its shelf life. Rheological evaluation should be done with a recording viscometer that continuously measures the shear throughout the hysteresis loop.

The critical nature of the flow properties of parenteral suspensions becomes apparent when one remembers that those products are frequently administered through 1- to 1.5-in or longer needles, having internal diameters in the range of only 300 to 600  $\mu\text{m}$ . In addition, microscopic examination shows a very rough interior needle surface, further hindering flow. The flow properties of parenteral suspensions are usually characterized on the basis of syringeability or injectability. Syringeability refers to the handling characteristics of a suspension while drawing it into and manipulating it in a syringe, clogging and foaming tendencies, and accuracy of dose measurement. The term injectability refers to the properties of the suspension during injection. It includes such factors as pressure or force required for injection, evenness of flow, aspiration qualities, and freedom from clogging. The syringeability and injectability characteristics of a suspension are closely related to viscosity and to particle characteristics.

**Emulsions.** An emulsion is a heterogeneous dispersion of one immiscible liquid in another.

This inherently unstable system is made possible through the use of an emulsifying agent, which prevents coalescence of the dispersed droplets (104). Parenteral emulsions are rare because it is necessary (and difficult) to achieve stable average droplets of less than 1  $\mu\text{m}$  to prevent emboli in the blood vessels. In addition, they are also thermodynamically unstable

by nature, that is, on standing they will eventually separate into two phases. However, proper choice of emulsifier (generally 1–5%) and optimum preparation conditions can delay the separation of phases and thus lead to more desirable nominal shelf lives of >2 years. An emulsion can be characterized as oil-in-water (o/w), containing up to 40% oil or water in oil (w/o), depending on the identity of the dispersed and continuous phases (105).

Preparation of an emulsion requires mixing the two immiscible phases with the surfactant(s) and applying energy (generally mechanical) in order to create shear forces to deform the interface and form droplets, using sufficient force and/or time to achieve the required droplet size. This can be done in either batch or continuous modes of operation. Typically, the surfactant or mixture of surfactants is dispersed in the aqueous phase along with any water-soluble components by stirring and heating as necessary until a homogeneous mixture is formed. The oil phase is then added with stirring or shaking to form a “premix” with large (>10 µm) droplets, which is then subjected to a high-energy mechanical homogenization. The final droplet size depends on the formulation composition as well as the operating conditions (e.g., temperature, homogenization pressure, and duration of homogenization) (106). The preferred method for sterilization of parenteral emulsion is terminal autoclaving. If the components of a particular drug-emulsion formulation preclude autoclaving because of stability problems, sterile filtration of the product may be a viable alternative, requiring that the emulsion droplets pass through a 0.22 µm sterilizing membrane filters. Apart from the requirements of sterility and absence of pyrogens, parenteral emulsion product must show acceptable physical stability properties such as particle (droplet) size distribution, viscosity, osmolarity, and zeta potential, as well as good chemical stability.

Parenteral emulsions are used for several purposes, including

1. water-in-oil emulsions of allergenic extracts (given subcutaneously),
2. oil-in-water sustained-release depot preparations (given intramuscularly), and
3. oil-in-water nutrient emulsions (given intravenously).

IV oil-in-water nutrient emulsions provide the source of calories and essential fatty acids for patients requiring parenteral nutrition for extended periods of time (usually for longer than five days). IV fat emulsions are prepared from either soybean (5–30%) or safflower oil (5–10%) and provide a mixture of neutral triglycerides, predominantly unsaturated fatty acids. The major component of fatty acids are linoleic, oleic, palmitic, stearic and linolenic acids. In addition, these products contain 1.2% egg yolk phospholipids as an emulsifier and glycerol to adjust tonicity. The emulsified fat particles are approximately 0.4 to 0.5 µm in diameter, similar to naturally occurring chylomicrons. The prime destabilizers of emulsions are excessive acidity (low pH) and inappropriate electrolyte content. Careful consideration must be given to additions of divalent cations (calcium and magnesium) which cause emulsion instability (107). Amino acid solutions, on the other hand, exert a buffering effect protecting the emulsion (108).

For IV oil-in-water nutrient emulsions, the current USP (1) specifies special requirement for the globule size: The volume-weighted, large-diameter fat globule limits of the dispersed phase, expressed as the percentage of fat residing in globules larger than 5 µm (PFAT5) for a given lipid injectable emulsion, must be less than 0.05%.

**Liposomes.** Liposomes are small, spherical vesicles which consist of amphiphilic lipids enclosing an aqueous core. The lipids are predominantly phospholipids which form bilayers similar to those found in biomembranes. Depending on the processing conditions and the chemical composition, liposomes are formed with one or several concentric bilayers.

Liposomes are often distinguished according to their number of lamellae and size. For example, small unilamellar vesicles (SUVs), large unilamellar vesicles (LUVs), and large multilamellar vesicles (MLVs) or multivesicular vesicles (MVVs). SUVs show a diameter of 20 to approximately 100 nm. LUVs, MLVs, and MVVs range in size from a few hundred nanometers to several microns. The thickness of the membrane (phospholipid bilayer) measures approximately 5 to 6 nm (109).

Liposomes are unique as drug carriers in that they can encapsulate drugs with widely varying polarities. Liposomal formulation can significantly increase the apparent aqueous solubility of a lipophilic drug, making possible delivery of a dose much higher than its water solubility. Therefore, a stable formulation with a water-insoluble drug is often achievable with no precipitation upon dilution. Drugs formulated in liposomes distribute differently in the body than conventional pharmaceuticals, since liposomes have distinct pharmacokinetic pathways of distribution and elimination (110). Encapsulation of drugs in liposomes thus results in an increase of drug levels at the targeted sites, such as inflammation, infection, or neoplasm, compared with the conventional formulations. This site-specific action reduces the toxicity of drugs without loss of their efficacies (111,112).

Phospholipids are the principal raw material of forming liposomes. These are susceptible to hydrolysis and oxidative degradation, latter due to unsaturated acyl chains. Large liposomes form spontaneously when phospholipids are dispersed in water above their phase transition temperature. The preparation of SUVs starts usually with MLVs, which then are transformed into small vesicles using an appropriate manufacturing technique.

Mechanical dispersion method is the most frequently used in the production of the large-scale liposomes. Usually it is two-step process: the film preparation and hydration step, and the particle size reduction step. The hand-shaken method and proliposome method are the two commonly used methods in the first step. For particle size reduction, sonication or microfluidization techniques are used. The liposomal preparations are then aseptically filtered through 0.22  $\mu\text{m}$  membrane filter to render them sterile for IV use since both lipids and the structure of liposomes are unstable at high temperatures and hence conventional terminal steam sterilization is not suitable.

Currently, there are two liposomal formulations approved for the U.S. market by the FDA: AmBisome<sup>®</sup>, a liposomal formulation of amphotericin B, and DOXIL<sup>®</sup>, a liposomal formulation of doxorubicin.

**Nanosuspensions.** Nanosuspension can be defined as colloidal dispersion of nano-sized drug particles that are produced by a suitable method and stabilized by a suitable stabilizer. Nanosuspensions are used to formulate drugs that are poorly water soluble as well as poorly lipid or organic solvent soluble. A number of reports have been published on the nanosuspension development in general (113-116), nanosuspension based injectable products (117-121), and their preclinical and clinical aspects (122). Major advantages of nanosuspensions for IV use are (i) avoidance of organic cosolvents, (ii) capability of packing higher mass-per-volume per dose, and (iii) potential stability improvement due to presence of unsolubilized solid-phase drug.

Nanosuspensions of drugs are typically produced either by controlled crystallization or by a high-energy particle size reduction process. Examples of the latter include wet milling and high-pressure homogenization (115,116). A third approach was reported recently, wherein crystallization and particle size reduction were combined to produce injectable nanosuspensions (117). Some of the important considerations in development of injectable nanosuspensions include: a) Nanoparticles should be stable and not susceptible to phenomena such as aggregation or Ostwald ripening, b) The nanosuspension should be free of contamination from any media used during processing, c) The nanoparticle manufacturing should be possible by aseptic processing, if terminal sterilization by heat or membrane filtration is not feasible, and d) Surfactants and excipients used should be acceptable for injectable applications.

Particle size distribution and its stability is an important element in the formulation in nanosuspension and requires careful optimization of surfactants to be used in the formulation. Adsorption kinetics and affinity of the surfactant to the newly formed crystal surface play a determining factor on the final particle size and stability of the nanosuspension. A number of surfactants have been explored for the stabilization of nano-crystals including polysorbates, phospholipids, phosphatidylcholine, etc.

Recently, a nanosuspension product containing Paclitaxel (a very water-insoluble anticancer agent), Abraxane<sup>®</sup>, has been approved by FDA for IV administration. Abraxane

contains lyophilized particles with 10% (w/w) paclitaxel and 90% (w/w) albumin. The particle size of the suspension is about 130 nm (123). Another example of IV nanosuspension is sterile powder of busulfan, encapsulated in a mixture of phospholipids - dimyritoylphosphatidylcholine and dilauroylphosphatidylcholine - in a buffer containing mannitol (124).

**Dried forms.** Sterile solids are drugs or drug products packaged in a dry form which must be reconstituted or suspended in sterile vehicle prior to administration. Many drugs, particularly the cephalosporins and penicillins, are not sufficiently stable in aqueous solution to permit packaging them "ready to use." The dry solids which are intended to be reconstituted by the addition of suitable solvents to yield solutions, conforming in all respects to the requirements for injections (solutions for injection), are described by a title in the form "for injection or sterile." Examples are thiopental sodium for injection (USP), in which the preparation contains added substances in addition to the drug, and sterile nafcillin sodium (USP), in which there are no additional ingredients other than the drug. In any such labeling, the product is intended to be appropriately reconstituted as a solution. Some reconstituted products must be further diluted prior to use, an example being methohexital sodium for injection (1).

Dry products which are to be reconstituted as suspensions by the addition of a suitable vehicle to yield a product meeting all requirements for sterile suspensions are labeled as "sterile for suspension." An example is sterile ampicillin trihydrate for suspension. Such preparations are manufactured and packaged as dry sterile solids by sterile filtration and freeze-drying or bulk sterilization and aseptic powder filling. The sterile bulk powder in the latter process can be achieved by either aseptic crystallization or spray-drying.

The powder filling procedure is briefly described below.

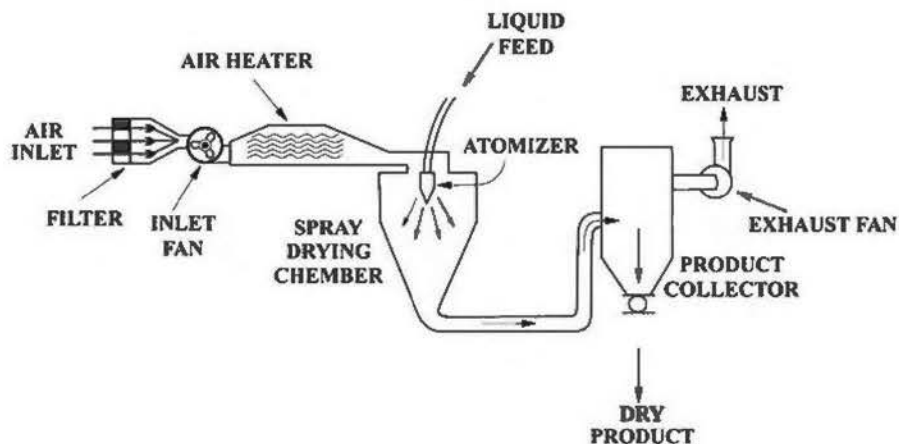
**Powder filling.** This method involves filling sterile powder into individual containers (vials) under aseptic conditions in which a measured quantity, either on a weight or volume basis, is delivered. If the material is free flowing, a machine method is used whereby the solid material is fed from a hopper to the container by means of an auger in the stem of the hopper or an adjustable cavity in the rim of a filling wheel.

Particle size and shape are important factors in powder filling since electrostatic charge, hygroscopicity, and flow are generally influenced by these properties. Additionally, the dissolution rate can be influenced by particle size. The humidity of the filling room should be carefully controlled. If the room is too dry, the powder will become electrostatically charged and will not flow. If the humidity is too high, compaction will occur because of moisture in the powder.

For parenteral products, the powder is generally prepared under aseptic conditions by crystallization or spray-drying, which provides greater assurance of sterility within the material. In the crystallization technique, the drug is dissolved in an appropriate solvent and sterilized by 0.2  $\mu\text{m}$  membrane. Next, under controlled conditions, another sterile solvent in which the drug is not soluble is added to the solution to induce crystallization of the drug. The sterile crystals are removed, washed and dried, then usually tested for particle size distribution, dissolution rate, and correct crystalline form prior to filling.

In order to obtain a uniform product from lot to lot, strict adherence to the procedures developed for a particular crystallization must be followed, including control of pH, rates of addition, solvent concentrations, purity, temperature, and mixing rates. Each crystallization procedure has to be designed to ensure sterility and minimize particulate contamination. Subtle changes, such as using absolute ethyl alcohol instead of 95% ethanol during the washing step of crystallization procedure, can destroy the crystalline structure if the material being crystallized is a hydrate structure.

If the drug powder is to be prepared by spray-drying, as shown in Figure 14, a sterile solution of the drug is prepared in a similar manner as for aseptic crystallization but instead of crystallizing the drug by adding another solvent, the sterile solution or a resultant slurry is sprayed through an atomizer with a fine orifice into a drying chamber, generally conical in shape.



**Figure 14** Schematic representation of spray drying process.

Upon contact with a stream of hot sterile gas, the solvent rapidly evaporates and the resulting powder is collected in a sterile chamber. The type of atomizer and method of spraying, the concentration of the solution to be sprayed, the pressure at which it is atomized and the temperature and pressure of the gas in the chamber are factors that influence the particle size and porosity of the resultant powder. The drug powder, present as hollow spheres, is then filled into vials as a dry powder.

**Freeze-drying or lyophilization.** The freeze-drying or lyophilization of injectable products is described in sufficient detail elsewhere (chap. 17, volume 2), so only a brief discussion will be included here.

Freeze-drying, also known as lyophilization, is widely used for pharmaceuticals to improve the stability and long-term storage stability of labile drugs (125-127). Freeze-dried formulations not only have the advantage of better stability, but also provide easy handling (shipping and storage). There are currently more than 125 small molecule lyophilized injection products in the market and the number of lyophilized proteins and vaccines exceeds 50 (128). Most of these are formulated as lyophilized products because of their instability in aqueous solutions, however, as in the case of acyclovir sodium, lyophilization is necessary to minimize interaction of the alkaline formulation with glass material. Table 17 shows the examples of products of whose aqueous stability was only for few hours, but once they were converted into dry product by lyophilization, the resulting products had acceptable market shelf life.

**Table 17** Comparison of Stability of Lyophilized and Solution Forms

Product	Bulking agent	Lyophilized product	Reconstituted product
Actreonom/Azactam	Arginine	3 yr	2 days (RT)
Amphotericin/Fungizone		2 yr	1 day (RT)
Cyclophosphamide/Cytoxan	Mannitol	3 yr	1 wk (13% loss)
Carboplatin/Paraplatin	Mannitol	2 yr	Particulates
Fosaprepitant/Emend	Lactose	>2 yr	24 hr at RT
Gemcitabine/Gemzar	Mannitol	>2 yr	24 hr at RT
Lansoprazole/Prevacid	Mannitol	>2 yr	1 hr at RT
Ixabepilone/Ixempra	None	>2 yr	1 hr at RT

Although there are those who would consider freeze-drying only as the last resort, there are others who view it as a panacea - a way to get into clinical trials quickly or a way to exclude contaminants and inert particles, especially in comparison with powder filling. Certainly, freeze-drying does offer the advantage over powder filling of accuracy of dosage, since the drug is filled into the final container as a solution. Microgram quantities can be filled precisely. The desired characteristics of a freeze-dried pharmaceutical dosage form include

1. an intact cake occupying the same shape and size as the original frozen mass,
2. sufficient strength to prevent cracking, powdering, or collapse,
3. uniform color and consistency,
4. sufficient dryness to maintain stability, and
5. sufficient porosity and surface area to permit rapid reconstitution.

Of course, as with any injectable dosage form, freedom from contamination (i.e., micro-organisms, pyrogens, and particulates) is an essential attribute. The desired characteristics can be achieved by proper formulation of the product and by employing optimum freeze-drying cycles.

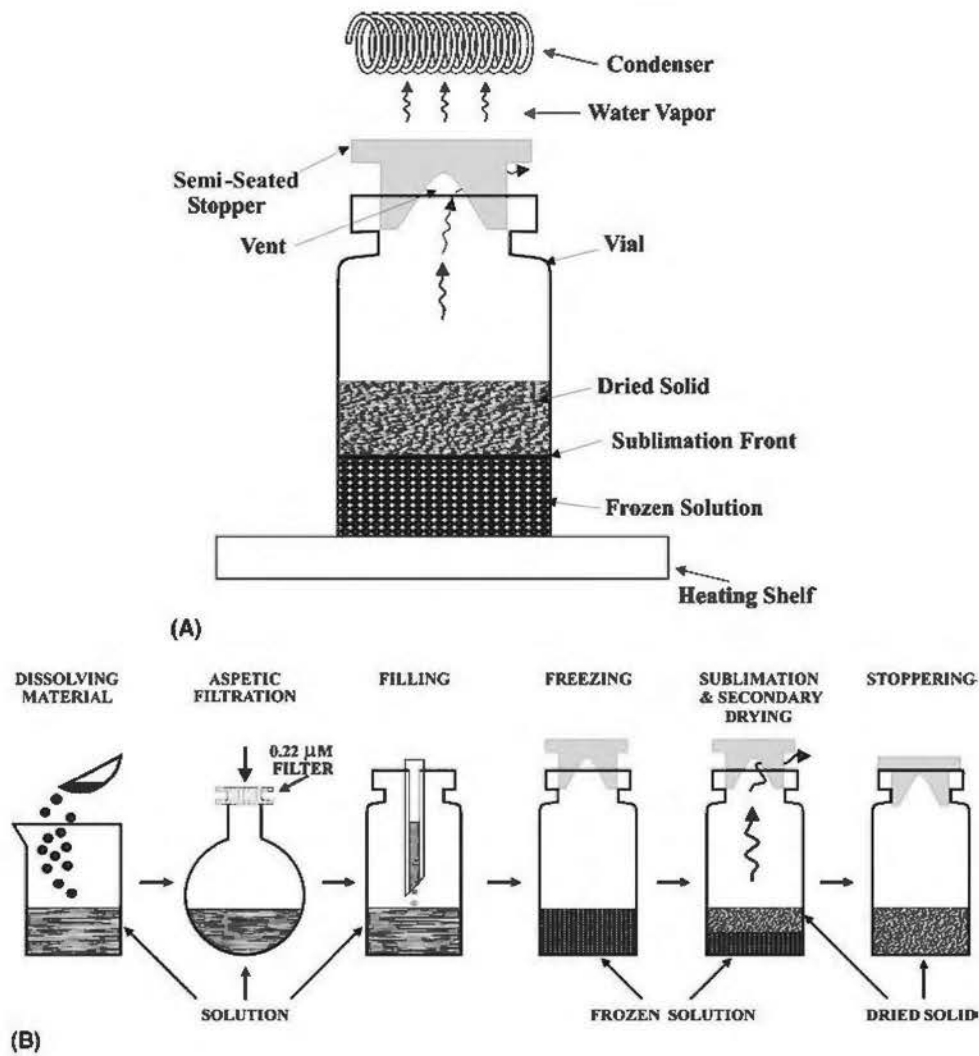
A freeze-drying cycle essentially consists of three distinct phases: a) Freezing of the solution, b) primary drying or sublimation, and c) secondary drying. Loading of the filled vials in the chamber, maintenance of vacuum throughout the drying phases, supply of refrigeration during freezing and heat during the drying phases, and completion of the drying cycle by stoppering the dried vials and unloading them out of chamber are some other required actions. For a systematic approach to the development of a suitable freeze-dried product, knowledge of the various stages of the process is necessary. Comprehensive reviews of principles and practice of freeze-drying in pharmaceutical are widely reported in pharmaceutical literature (129-132).

The initial freezing process is of critical importance since it will influence the pattern of the sublimation phase. During freezing, pH change may arise from crystallization of buffer salts as well as large increase in ionic strength that may result into stability problems. The pH shift during freezing can be minimized by optimal choice of buffer salts or by reducing buffer concentrations. Upon freezing, the entire formulation must be in a completely frozen state otherwise collapse or meltback may happen during drying. The temperature above which the freeze-dried product loses macroscopic structure and collapses during freeze-drying is termed as collapse temperature or  $T_c$  and is usually about 2°C higher than  $T_g'$ , which is often associated with the glass transition temperature in the frozen state (133).  $T_c$  equals the eutectic temperature ( $T_{em}$ ) if solutes are crystallized in the frozen solution. Well designed cooling cycle (ramp and hold times) must be used in order to obtain an appropriate structure of the frozen mass, which is a function of the rate of freezing and the final freezing temperature. The rate of freezing affects the size of ice crystals. Slower rate of freezing results in larger ice crystals and vice versa. If the frozen system exhibits metastable or amorphous-glassy structures, these structures may need to be ruptured by appropriate thermal treatment or annealing process (a succession of cooling and rewarming periods), thereby inducing crystallization of the amorphous material for efficient sublimation.

Most freeze-dried drug products are organic electrolytes which exhibit eutectic points or glass transition temperatures and super-cooling tendencies. Several methods have been used for determining eutectic temperatures: (i) thermal analysis, (ii) differential thermal analysis, and (iii) electric resistivity (131).

Knowledge of the eutectic temperature of the additive is essential since the addition of a salt such as sodium chloride to a drug with a eutectic significantly above that of sodium chloride would only succeed in lengthening the cycle because lower temperatures would have to be maintained. In addition, some additives, such as the phosphates, tend to form crusty-appearing cakes. This occurs during freezing and drying, probably because of the phenomenon of recrystallization. Volatile substances are generally considered to be of little value to the finished cake but can be used if they accelerate the drying cycle, for example, t-butanol (134,135). The next step in the freeze-drying process is primary or sublimation drying which is





**Figure 15** Schematic representation of freeze drying process.

conducted under low chamber pressure conditions, for example, 200 mTorr or lower, under which sublimation of ice, as dictated by the ice/water-vapor equilibrium line of the phase diagram of water, takes place and the water vapor from the frozen matrix is transferred out of the vial, traveling into the headspace of the vial, through the vents of the closure, into the chamber, and eventually onto the cold condenser, where it is condensed again as ice (Figure 15A). Thus, frozen water from the vial is vaporized by sublimation and collected on the cold plates of condenser. The sublimation is a phase change, requiring energy, which must be supplied as heat from the carefully controlled heated shelf. The sublimation drying phase is a combined heat-mass transfer process in which both the transfer phenomena must be carefully balanced so that sustained drying rate (mass transfer) prevails without collapsing or melting of the frozen mass because of accumulation of heat from the heated shelf (heat transfer). During

the entire sublimation phase, the product temperature should always be several degrees below  $T_c$  in order to obtain a dry product with acceptable appearance. Factors influencing the rate of vaporization have been discussed extensively (136-139). The faster heat can be applied, the faster the drying proceeds, provided that, a) The temperature of the product remains below its liquefying point, and b) sufficiently low pressure is maintained in the system by efficient vacuum pumps. If a sufficiently low pressure is not maintained, the temperature of the product will rise resulting in the partial softening or puffing of the product.

In developing a formulation for freeze-drying, the optimal formula will permit the overall cycle to be carried out in the least amount of time, while providing a stable and efficacious product which contains a low moisture content, undergoes rapid reconstitution, and possesses the desired appearance. The potency of many lyophilized products is so high that relatively small amounts are required for the lyophilized injectable dosage form. Therefore, the need for suitable filler or bulking agent is often indicated. The percentage of solids in the frozen plug will vary depending on the dosage and nature of the active ingredient; generally, it should be above 5% and not exceed 30%, with a 10 to 15% content being optimum. Materials to choose from to add to the solution to improve the physical characteristics of the finished cake are limited but include mannitol, lactose, sucrose, dextran, amino acids, sorbitol, gelatin, mono- and dibasic sodium phosphate, albumin, sodium chloride, etc. It should be kept in mind when adding bulking agents that drying will be accelerated if the solute concentration is kept low. However, solutions with too low concentration ( $\leq 1\%$  w/w) may result in very brittle cake and there is a likelihood that some of the powder may fly off the cake into the chamber resulting in low drug content in the vial.

If degradation is a risk during freezing due to concentration effects or pH changes, stabilizers or buffers may have to be added. The problem of collapse has been discussed earlier (140) and if the substance is vulnerable to collapse, a rigidizer such as glycine or mannitol may need to be added. If damage during freezing is a problem, a cryo-protective agent such as sucrose or albumin may be added. If the ingredients that are added are found to adhere to the glass surface, such as albumin, then the containers with thin walls, such as ampuls and tubular vials, may need to be coated with silicone to minimize sticking. The depth of fill in a container is critical. While this depends on the volume of the container, a rule of thumb has been 1 to 2 cm in depth but never exceed one-half the capacity of the container otherwise breakage of vials may be seen.

Freeze-dried products are generally packaged in ampuls or vials. Ampuls would only be used for single-dose administration, and provide even drying because the tubing is thin and bottoms are reasonably flat. However, they must be sealed after removal from the chamber and reconstitution is sometimes cumbersome if shaking is required. Additionally, the generation of glass particles is a problem. Vials are used for both single- and multiple-dose application. If molded glass is used, there is greater incidence of variation of thickness and uneven bottoms. The containers must be sealed with a closure that can be accomplished inside the chamber, lessening the risk of contamination and providing an opportunity to seal under an inert gas or under vacuum.

The next stage in freeze-drying cycle is secondary drying. When sublimation drying phase is completed, the temperature of the product progressively rises (following the temperature of the shelves). The goal of desorption is to remove traces of moisture in the product (the majority of the water in the form of ice already been removed during the sublimation phase). The secondary drying process consists in removing the molecules by having the product under the highest possible shelf temperature (e.g., 20-35°C) compatible with its stability and the chamber pressure at its lowest value.

Typical process of freeze-drying is illustrated in Figure 15B. It involves: (1) dissolving the drug and excipients in a suitable solvent, generally water; (2) sterilizing the bulk solution by passing it through a bacteria-retentive filter; (3) filling into individual sterile containers with semi-stoppered closures; (4) freezing the solution by placing the open vials on cooled shelves in a freeze-drying chamber, (5) applying a vacuum to the chamber and heating the shelves in order to sublime the water from the frozen state, and (6) breaking the vacuum at

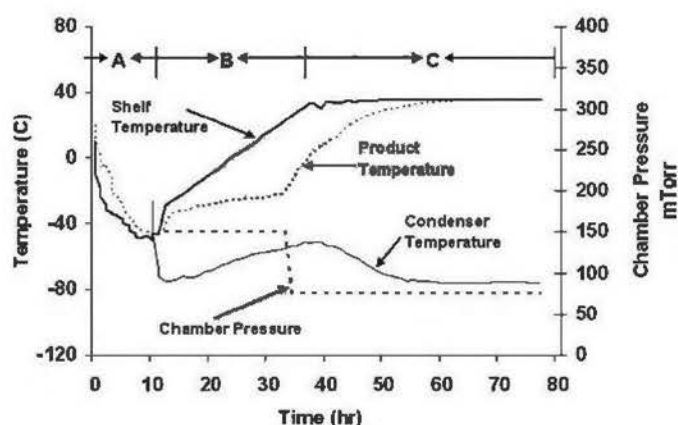


Figure 16 Typical product temperature/chamber pressure curve during freeze drying.

the end of drying using sterile air or nitrogen, fully stoppering the containers, and unloading of the vials.

Temperature and pressure curves for a typical cycle are illustrated in Figure 16 for Mannitol solution (5% w/w) filled into 10 mL glass vial (5 mL/Vial). Freezing stage is denoted by "A," primary drying by "B," and secondary drying by "C." During freezing as the shelf temperature is lowered the product cools down and freezes and eventually reaches its target temperature of  $< 40^{\circ}\text{C}$ . At this time, the condensers are chilled to below very low temperature ( $< 70^{\circ}\text{C}$ ) and the vacuum is initiated in the chamber. Once the vacuum has reached its target value, say 150 mTorr in this case, then the primary drying begins wherein the shelf is heated slowly to provide heat to sustain sublimation. Around 34 hours, at the end of phase "B," the product temperature starts rising swiftly indicating that the ice is removed and the heat is consumed not just for the phase change in sublimation, but results in increase in the temperature of the product. The phase denoted by "C" is secondary drying where the continuously heated shelves provide heat to remove residual moisture by desorption process, aided by lower chamber pressure than before. At the end of secondary drying, the vials are fully stoppered, vacuum is broken to return the chamber to the atmosphere and the vials are unloaded.

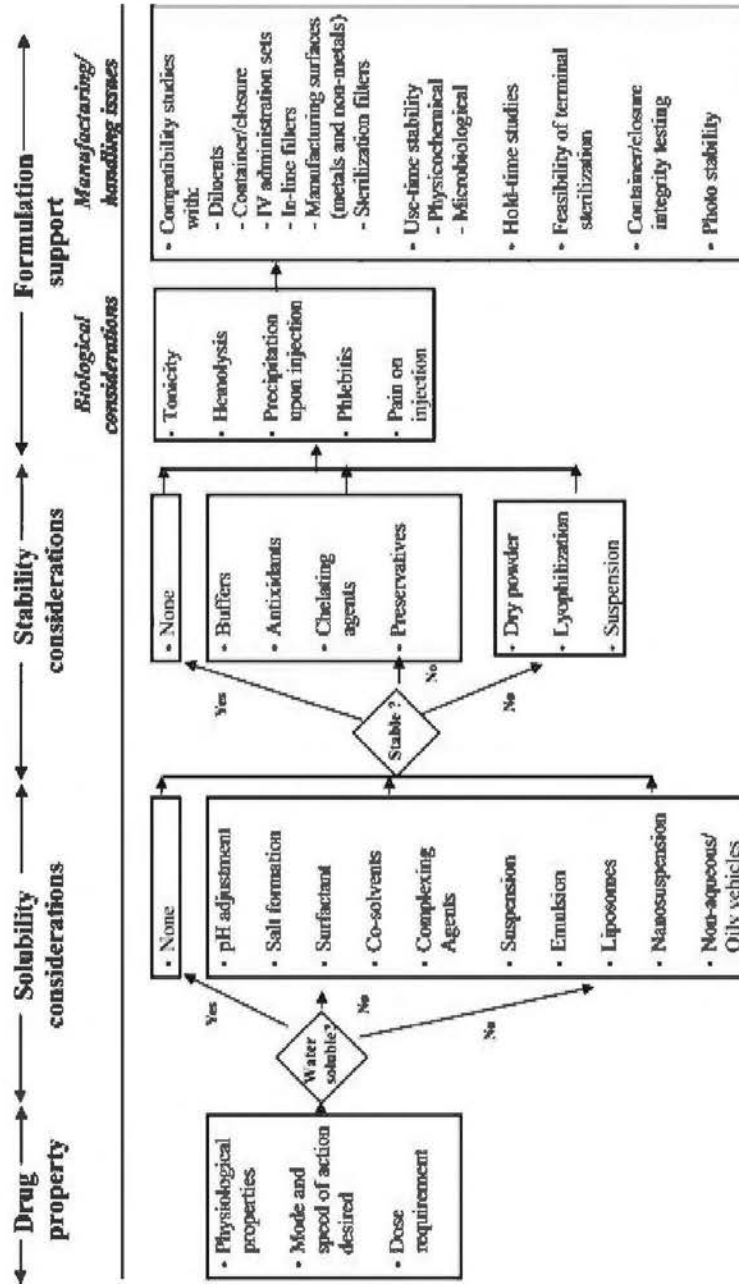
#### Formulation Development Process

From preceding sections, it is clear that successful formulation of an injectable small-volume preparation requires a broad knowledge of physical, chemical, and biological principles as well as expertise in the application of these principles. Moreover, formulation is a highly specialized task requiring not only specific knowledge but also years of experience. During the course of development, formulation design and optimization is an iterative process and evolves as the product moves from the discovery to clinical to commercial stages. Although, most of the times, the development is an empirical approach based on principles mentioned earlier, there are number of strategies or decision trees that one can adopt to proceed with the product design. There are even published reports that suggest use of "expert systems," comprising of databases and decision making processes, to aid parenteral development (141).

Table 18 summarizes one such approach that can be considered as a template for parenteral formulation development process which considers many of the essential factors necessary for the formulation design and lists various formulation-supporting studies that are needed from patient use, manufacturing, and marketability point of view. These

Downloaded from informahealthcare.com by McGill University on 01/15/13  
For personal use only

Table 18 Suggested Template for Small-Volume Injectable Formulation Development Process



studies are not mutually independent, though. Not only the formulator must arrive at an optimum formula from stability/solubility point of view alone, but he/she must ensure that the product is acceptable from patient's acceptability/tolerance point of view and it poses minimal difficulty or constraints from the manufacturing and/or marketing point of view.

**Formulation-supporting studies.** In finalizing the formulation, a number of supporting studies are needed to address the biological or patient-related issues, support the manufacturing process, and define the boundaries under which the product's qualities will be maintained throughout the shelf life of the product.

1. Biological considerations:
  - a. Evaluation of impact of formulation toward hemolysis, precipitation, phlebitis, and pain on injection
  - b. Tonicity
2. Manufacturing and handling support studies:
  - a. Compatibility with commonly used diluents and IV administration sets, etc.
  - b. Compatibility with manufacturing equipment
  - c. Compatibility with membrane filters, if aseptic processing is used during the manufacture
  - d. "In-use" stability studies
  - e. Feasibility of terminal sterilization
  - f. Photostability

**Biological considerations.**

**Hemolysis, precipitation, phlebitis, and pain on injection** Some injection products are prone to formulation-related problems such as hemolysis of the RBCs; precipitation of the drug and ensuing phlebitis; and pain at the site of injection.

Hemolysis results from disintegration of RBC membrane and release of the cellular contents into the plasma, particularly that of hemoglobin. Once outside of the RBC, hemoglobin molecule quickly dissociates into its component polypeptide chains which can pose many serious physiological problems, mainly the renal failure. Hemolysis usually results from hypotonicity or from the effect of drug or the formulation components on cell membranes (142,143).

Precipitation of the drug at the site of administration can happen once the solubilizing principles are diluted away or removed from the vicinity of the drug.

Phlebitis occurs because of inflammation of a vein with symptoms such as tenderness, edema, erythema, and a local temperature rise. In severe cases, it can lead to thrombus and even more severe complications. Although a number of factors have been implicated as causes of phlebitis; particulate matter, precipitation of drug, and local pH effects are the most likely causes (144-148).

Injectable formulations are often painful and irritating following injection as a result of cell damage such as phlebitis. Sometimes the pain/irritation response is associated with the active drug (s) present in the formulation, for example, macrolide antibiotic (149) and excipients (150). Pain on injection may occur during and immediately following the injection or it may be a delayed or prolonged type of pain which increases in severity after subsequent injections. The actual cause of the pain is often unknown and will vary significantly among patients according to the product. In some cases pain may be reduced by minor formulation changes such as adjusting tonicity and pH or adding an anesthetic agent such as benzyl alcohol or lidocaine hydrochloride. In other cases pain is more inherent to the drug and the problem is more difficult or impossible to resolve. Pain, soreness, and tissue inflammation are often encountered in parenteral suspensions, especially those containing a high amount of solids. A number of in vivo (animal studies) and in vitro studies to evaluate hemolysis, precipitation, phlebitis and pain upon injection have been published (151-154). It is important that the

formulator evaluate the potential of the formulation to causes of the above mentioned problems using these or other suitable techniques.

**Tonicity** Tonicity has been previously discussed under “Added Substances.”

**Manufacturing and handling support studies.**

**Compatibility with commonly used diluents and IV administration sets** Many IV parenteral products are often administered via large-volume parenteral (LVP) solutions. In such cases, the solubilized portion of the product, either withdrawn directly from the ready-to-use solution or from the reconstituted dry product, is directly added to the diluent bag or added through the Y-site of the IV administration set. Obviously, the potential for drug stability and compatibility problem is great because of the long duration of contact time and exposure to ambient conditions of temperature and light (155). The potential physical and chemical incompatibilities associated with such dilutions are compiled in a treatise by Trissel (74) and is often the primary reference book on this subject in the practice of pharmacy.

Typically, compatibility of the drug product with the reconstitution diluents (precipitation and stability), at the recommended storage temperature and at the likely extreme concentrations of administration, is demonstrated with most commonly used diluents and IV fluids, such as normal saline, dextrose solutions, ringer’s solution, etc., and combinations thereof (156). It is also important that compatibility information is generated for the drug in contact with potential delivery devices such as the IV administration sets, in-line filters, syringes, etc.

**Compatibility studies with manufacturing equipment contact surfaces** Various contact surfaces are encountered during the manufacture and storage of injection products. Compatibility studies of the drug product with such surfaces must be evaluated to ensure that there are no adverse interactions and the quality of the product is unaffected. Typical product contact surfaces during the manufacture are transfer tubing, manufacturing equipment, filtration surfaces and devices, filling machine parts (pumps, filling needles) surfaces, etc. These are comprised of variety of materials such as rubber, plastic, ceramics, and metals. Typically, the component under investigation is placed in contact with the drug product solution for 24 to 96 hours at room temperature, at which point the samples are analyzed for various physicochemical attributes such as pH, appearance, UV/FT-IR spectroscopy, and potency.

**Compatibility with packaging components** During the storage of the product in the final container, the product comes in contact with the rubber-based or polymeric stoppers, glass in the case of vials, or other plastic materials in the case of syringes and plastic bags. Compatibility studies of the drug product with such packaging components is performed similarly by contacting the packaging components with the drug product and analyzing for physicochemical attributes of both the solution and the components.

**Compatibility with membrane filters** Bulk solutions of many aseptically produced injection products are sterilized by membrane filtration using 0.22  $\mu\text{m}$  filters. It is important that the compatibility of the drug product with that of material of the sterilization membrane filter (and prefilter, if used) as well as the filter assembly is evaluated to ensure that the product quality is not affected as well as no undesired components are added to the drug product. Some of the techniques used in practice for this purpose include the following:

1. Microbial membrane retention testing to demonstrate that the formulation of the product does not adversely affect the effectiveness of removal of any microbial contamination from the bulk solution. This is typically done by filtering a challenge solution containing large number of bacteria in the drug product solution (or its equivalent placebo) and testing for the filtrate for any microbial presence.
2. Membrane compatibility study to ensure that the prolonged exposure of the product does not affect the key membrane characteristics. This is typically done by soaking the membrane disks in the drug bulk solution for 24 to 48 hours and then evaluating

- the filters for key parameters such as water permeability (flow rate), product bubble point, weight change, and appearance.
3. Filter extractability testing to assess the effect of formulation on the extractables from the filter. This is typically performed by subjecting the filter device to worst-case sterilization conditions (time, temperature, and repeated cycles) followed by extended exposure to organic solvents such as 100% denatured ethanol and then analyzing the extract for volatile and nonvolatile organic compounds.
  4. Product specific bubble point measurement as a tool to monitor the integrity of the filter during routine manufacturing.

**“In-use” stability** Use-time stability studies are performed to establish the following:

1. How long the drug product solution is stable at ambient (use) conditions, if normally the drug product is supplied in dried form.
2. How long the drug product is stable at ambient (use) conditions, if normally kept at refrigerated storage.
3. In what diluent and how long the diluted drug solution is stable, from both physicochemical and microbiological perspectives.

The above information is then included in the package insert that is provided with the final drug product and forms the basis for the proper use of the drug and instructions for suitable use of diluents and delivery devices.

**Feasibility of terminal sterilization** Injection products are rendered microbiologically sterile by terminal sterilization by using steam or dry heat. Steam sterilization, which offers the greatest assurance of sterility, can be expected to cause some changes in the product, however subtle. Drugs are reactive substances and autoclave temperature (121°C) for 15 to 30 minutes could give rise to degradation processes and interactions with the container. Additionally, materials could leach from the rubber closure. In addition to loss of drug, antimicrobial agents and antioxidants can be absorbed or consumed during sterilization. Lately, it is becoming a well-accepted principle that sterile drugs should be manufactured by aseptic processing only when terminal sterilization is not feasible because of excessive thermal degradation of the product. There are many categories of the products that may qualify for not subjecting to terminal sterilization (157); however, regulatory agencies may require a written justification to address why a product is not being terminally sterilized. With such restrictions, the formulator of an injection product must assess the effect of terminal sterilization conditions on the stability of the product, the acceptable level of degradants, and offer alternate sterilization techniques such as aseptic processing or adjunct processing step(s) in addition to aseptic processing, for example, addition of heat exposure condition which may provide increased level of sterility confidence (158).

**Photostability** Exposure to irradiation such as light can influence the stability of the formulation, leading to changes in the physicochemical properties of some products. The most obvious result of drug photodecomposition is a loss of potency of the product. In few cases, trace amounts of photodecomposition products formed during storage and administration may lead to adverse effects (159). The excipients used may also often contribute to the photoreaction (160-163) and hence stability evaluation in the presence of excipients is important. The selection of a protective packaging must be based on knowledge about the wavelength causing the instability. A review by Tonnesen (164) has focused on practical problems related to formulation and stability testing of photolabile drugs. An ICH guideline, “Guidelines for the photostability testing of new drug substances and products,” describes photostability methodology, including the decision flow-chart, choice of light source, sample preparations, and interpretation of results (165).

In the case of injection products, transparent glass or plastic vial offers little protection toward radiation (166). The stabilizing effect of amber glass as the only means of

photoprotection is not satisfactory for highly photolabile drugs like molsidomine (167). Even brown glass can offer inadequate protection as demonstrated for drugs like epinephrine, isoprenaline and levarterenol (168). In practice, a secondary container, such as a cardboard box or carton is often necessary to prevent photodegradation. Similarly, for extremely high light-sensitive drugs, the manufacturing operations (compounding, filling, and packaging) may also need to be carried out by minimizing light exposure or by using yellow lights in the process areas.

At the conclusion of the formulation development process, the formulator must be in a position to compile all the knowledge generated in the process for regulatory scrutiny. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) has published guidance for industry, "Q8 Pharmaceutical Development," which provides necessary elements of the development process that includes the concepts of quality by design (QbD), use of quality risk management, and use of knowledge management (156). This guidance recommends summarizing the development of the formulation including identification of those attributes that are critical to the quality of the drug product. As per the guidance, the summary should highlight the evolution of the formulation design from initial concept up to the final design. This summary should also take into consideration the choice of drug product components (e.g., the properties of the drug substance, excipients, container closure system, any relevant dosing device), the manufacturing process, and, if appropriate, knowledge gained from the development of similar drug product(s). The guideline further describes the use of principles of quality by design (QbD) during the development of a drug product. The QbD identifies characteristics that are critical to quality from the perspective of the patients, translates them into attributes that the drug product should possess, and establishes how the critical process parameters can be varied to consistently produce a drug product with the desired characteristics. Reader is encouraged to study and practice the quality principles laid down by this guidance.

#### **Container Effects on Formulation**

Containers for parenteral products serve several purposes; facilitate manufacturing; maintain product protection including sterility and freedom from pyrogen; allow inspection of the contents; permit shipping and storage; and provide convenient clinical use. The container components must be considered as integral parts of the product because they can dramatically affect product stability, potency, toxicity, and safety, and therefore must be evaluated carefully with a variety of tests. For details on this topic, reader is directed to chapters 11 and 12 of this book.

#### **Stability Evaluation**

Throughout the world, there has been phenomenal increase in laws, regulations and guidelines for reporting and evaluating data on safety, quality and efficacy of new medicinal products. Although different regulatory systems have the same fundamental concepts to evaluate the quality, safety and efficacy, the process of evaluation has diverged over time to such an extent that the industry has found it necessary to duplicate many time-consuming and expensive test procedures, in order to market new products, internationally. To address this, initiation of ICH was pioneered by the European Community, in the 1980s, and later joined by the representatives of the regulatory agencies and industry associations of the United States and Japan. The key goals of the ICH have been the development of the "ICH process" for developing harmonized guidance on technical issues and under this process many guidance have been published. For details on the topic of stability studies regarding the stability procedures, sampling requirements, storage conditions, testing schedules, and evaluation of data, reader is directed to chapter 10, volume 3 of this book.

#### **Process Effects**

The processing of parenteral products has been covered elsewhere in this textbook, but some specific cautions associated with the effects on formulation will be highlighted. There comes a



point in the development process of a product to characterize the production process and assess its effect on the formulation. This requires scale-up procedures to identify the process and equipment variables and with knowledge of the formulation and package variables assess how product quality and manufacturing productivity will be affected. In the manufacture of a sterile product, the assurance that the finished product possesses the desired quality control characteristics depends on a number of independent but interrelated events commencing with the initial design of the dosage form and carrying forth through the process design and validation and culminating with the establishment of standard procedures for manufacturing.

To provide for the assurance that all quality attributes will be achieved on a repetitive basis, the following are essential: (1) the dosage form is designed with knowledge of the desired functional and quality control characteristics of the finished product; (2) the qualification procedures are adequate to ensure reliability of the equipment, effectiveness of the process, and the integrity of the processing environment; (3) personnel are trained in contamination control techniques; and (4) there is adequate documentation of all procedures and tests. Such a development sequence combined with validation requirements suggests a formalized program culminating in a product that can be reliably processed. The process characterization is a principal step in assuring that the process can be translated to manufacturing on a routine production basis. Although this chapter is not intended to cover processing in the broad sense, those responsible for developing formulations should have an understanding of the following:

1. Scale-up procedures
2. Preliminary technical documentation
3. Design of processing and validation protocols
4. Use of process analytical technologies (PAT) for monitoring and control purposes
5. Qualification/validation runs
6. Final technical documentation and authorizations

The overall approach must be organized, scientific, and thorough. Moreover, the issues in shipment of the product, especially if refrigeration or some other storage temperature restrictions apply must be addressed. Lastly, addressing the usual unplanned deviations in the manufacturing processes and the provision of rework or rescue procedures must also be considered.

## FORMULATION OF LARGE-VOLUME INJECTIONS

### Introduction

LVPs or injections are primarily used for IV nutritional therapy which is required when normal enteral feeding is not possible or is inadequate for nutritional requirements. Specific nutritional requirements and administration mode depends on the nutritional status of the patient and the duration of the parenteral therapy (45). To meet IV nutritional requirements, one or more of the following nutrients may be required:

- Protein substrates: These include various amino acids formulation used for general replacement purpose, for hepatic failure, for encephalopathy, and for metabolic stress conditions.
- Energy substrates: These include dextrose and IV fat emulsion.
- Electrolytes: Saline, ringer's solution, etc.
- Vitamins and trace metal supplements.

Besides providing the water, electrolytes, and simple carbohydrates needed by the body, LVPs also a) act as the vehicle for infusion of drugs that are compatible in the solution, b) provide solutions to correct acid-base balance in the body, c) act as plasma expanders, d) promote diuresis when the body is retaining fluids, d) act as dialyzing agents in patients

with impaired kidney function, and e) act as x-ray contrast agents to improve diagnostic abilities. It is now almost a standard practice to begin infusing a patient with a LVP, often dextrose and electrolytes, shortly after admission to the hospital. One of the reasons for this is to provide a readily accessible link to the central compartment if additional medications are required, while at the same time providing fluids and electrolytes to achieve an optimum balance for further treatment. IV administration, however, bypasses protective mechanisms of the body, and the onset of adverse reactions, including the cases of nosocomial bacteremias in hospitals (169), which may come about from many causes, can be as rapid as the beneficial effects. The National Intravenous Therapy Association (NITA) as well as many technical books have developed recommendations for procedures to be followed during IV therapy (170,171). The procedures are designed to minimize undesired reactions.

### Formulation Principles

#### *Physiological Parameters*

The physiological parameters of a LVP formulation are limits on those characteristics of the solution that impart some effect on the biochemistry of the body.

Some constituents that are basic to the sustenance of life in the human organism can be influenced by IV therapy. These are water, electrolytes, carbohydrates, amino acids, lipids, and micronutrients such as vitamins, minerals, and trace elements.

The living cell, the body's basic unit, is bathed in tissue fluid kept constant in composition by the interaction of many processes, some of which are outside the scope of this chapter. Alteration in the amount or composition of tissue fluids can cause significant physiological derangements. Such imbalances may occur as a major or minor feature of illness, trauma, or surgical procedures. Under such circumstances it is necessary to anticipate and correct deficits and imbalances by administration of suitable fluids. The body fluids, named for the compartments in which they are found, are intravascular (within the blood vessels), intracellular (within the cells), and interstitial (within the space between cells). Extracellular fluid is the total of intravascular and interstitial fluids. The fluids consist of water containing a mix of electrolytes, neutral solutes in a wide range of high and low molecular weights, and undissolved substances. The composition of each fluid differs, yet a chemical balance is maintained in each fluid. Approximate figures for the electrolytic composition of body fluids are shown in Table 19.

**Table 19** Electrolyte Composition of Body Fluid Compartments

Electrolytes	Intravascular	Interstitial	Intercellular
	(mEq/L)	(mEq/L)	(mEq/L)
<b>Cations</b>			
Sodium (Na <sup>+</sup> )	142	145	10
Potassium (K <sup>+</sup> )	4	4	160
Calcium (Ca <sup>2+</sup> )	5	5	2
Magnesium (Mg <sup>2+</sup> )	2	2	26
Total	154	156	198
<b>Anions</b>			
Chloride (Cl <sup>-</sup> )	102	115	2
Bicarbonate (HCO <sub>3</sub> <sup>-</sup> )	27	30	8
Phosphate (HPO <sub>4</sub> <sup>2-</sup> )	2	2	120
Sulfate (SO <sub>4</sub> <sup>2-</sup> )	1	1	20
Organic acids	6	7	
Protein	16	1	48
Total	154	156	198

Extracellular fluid is characterized by high concentrations of sodium and chloride ions. The intravascular fluid contains a much higher concentration of protein than is found in interstitial fluid because the large plasma protein molecules are not diffusible. The retention of protein anions on one side of, the semi-permeable membrane causes a redistribution of the anions that are permeable, in order to maintain chemical balance (172). As a result, the concentration of other anions is lower in intravascular fluid than in interstitial. Intracellular fluid is characterized by very high concentrations of potassium, phosphate, and protein.

An LVP formulation must be developed to ensure that desired levels of the solution are administered in a therapeutically active and available form. In order to obtain the desired response, the physiological intent of the formulation must be considered and the physiological, chemical, and physical properties of the formulation defined. The formulator must understand the biochemistry of the body and the chemistry of the *in vivo* parenteral because it is through their interaction that the result is achieved. These factors are discussed in the sections to follow.

#### *Formulation Parameters*

**Physiological.** Body fluids rapidly exchange both water and electrolytes between the cells and extracellular compartments, maintaining equilibrium within and between the compartments. The movement of solvent and solute through the semi-permeable membranes that separate the compartments is called osmosis. If the concentration of solutes in adjoining compartments differs, water moves very rapidly into the compartment with the higher concentration in the effort to establish equilibrium. Simultaneously, disassociated solutes diffuse at a slower rate to the compartment with the lower concentration. Because some components of the fluid cannot move through the semi-permeable membrane, the fluid in the compartment must make adjustments to maintain its own ionic equilibrium (mentioned previously with respect to the difference in the ions contained in extracellular and interstitial fluids).

The resistance to unrestricted movement between compartments is defined as osmotic pressure and is expressed as osmoles per kilogram (osm/kg) or, more conveniently, milliosmoles per kilogram (mOsm/kg). Osmolarity values of dilute solutions can be calculated and their levels expressed as milliosmoles per liter (mOsm/L) by using the formula:

$$\text{mOsmol/L} = \frac{\text{g/L of solute}}{\text{molecular weight of solute}} \times 1000 \times \text{number of ions}$$

Sodium chloride, for example, has a molecular weight of 58.5 and forms two ions,  $\text{Na}^+$  and  $\text{Cl}^-$ , in solution. The osmolarity of 0.9% sodium chloride injection would be calculated as  $\text{mOsm/L} = 9/58.5 \times 1000 \times 2 = 307.7$ , rounded to 308.

An immediate concern of introducing large amounts of fluid into the body system is that of maintaining the "tone" of the living body cells, RBCs circulate in blood, which has an osmolarity of 306. Using osmolarity as a measure of tonicity, one would expect no physical change in the RBC if 0.9% sodium chloride injection, with an osmolarity of 308, were infused into the vein. This is the case, as can be demonstrated by putting red cells into the 0.9% Sodium Chloride Injection and microscopically examining the cells for physical change. No changes result, and the solution is termed isotonic. If RBC are placed in a hypertonic solution, for example, 20% dextrose (1010 mOsm/L), the water in the cell will diffuse out, causing the cell to shrivel. Conversely, RBC placed in a hypotonic solution, such as 0.45% sodium chloride (154 mOsm/L), will swell because of the flow of water into the cell and, if the effect is great enough, may rupture. For this reason, WFI, USP, which has no dissolved solids, despite its name is never injected alone. Table 20 shows the relationship between osmolarity and tonicity.

Tonicity, as defined by numerical calculation, is only one consideration that must be taken into account and it must be used with judgment. For example, a solution of 1.85% urea is isotonic but quite unsuitable for administration at the rate isotonic solutions are normally infused; it can cause hemolysis as well as upset the body's nitrogen balance. A solution of amino acids, which is hypertonic at about 850 mOsm/L, may be life sustaining and the

**Table 20** Relationship Between Osmolarity and Tonicity

Osmolarity (mOsm/L)	Tonicity
>350	Hypertonic
329–350	Slightly hypertonic
270–328	Isotonic
250–269	Slightly hypotonic
0–249	Hypotonic

problems of tonicity can be overcome if it is introduced slowly into a large vein where there is ample blood volume to assure dilution. Hypertonic and hypotonic solutions can be used if administered slowly. The rates of shift of water into or out of the vascular system are determined by the rate of administration, rate of diffusion of the solute, and tonicity of the solution. Calculation of tonicity has been described in the earlier section.

#### Physicochemical

**Solubility** Compared with the solubility challenges in compounds used in small-volume parenteral as described earlier, most of the solutes used in LVP solutions are extremely soluble relative to their therapeutic concentrations. This means that solubility is rarely a consideration during formulation and, once in solution, the ingredients remain dissolved under normal storage and handling conditions. There are occasional reports of crystallization in highly concentrated solutions, such as 15% mannitol; this is caused by a reduction in solubility when the bottle is cold and the crystals go back into solution readily when the bottle is warmed. The solubility of mannitol is 13 g/100 mL water at 14°C; the package inserts for mannitol solutions caution the user that concentrations over 15% may show a tendency to crystallize.

In some cases, as with amino acid or high-concentration dextrose solutions, the temperature of the WFI is elevated during mixing. Although the ingredients are soluble at lower temperatures, minimizing the preparation time reduces the time the solution is exposed to ambient microorganisms. The order in which ingredients are added to the mix tank may have an effect on how rapidly the mix is completed or whether it can be completed. For example, when one is preparing amino acid solutions the pH changes after the addition of each amino acid and some amino acids are soluble only at specific, narrow pH ranges. Consequently, the order of adding the various amino acids can be critical unless preblended powdered amino acids are used. In general, solubility only becomes a consideration when the LVP is used as a carrier for other drugs.

**pH** The pH of a formulation must be considered from the following standpoints: the effect on the body when the solution is administered; the effect on stability of the product; the effect on the container closure system, and the possible degradation of drugs that are added. The pH of blood is normally between 7.35 and 7.45, and the immediate effect of intravenously introducing fluids outside this range depends on the buffer capacity of the solution, determined by the amount of weak acids or bases that are part of the formulation. The solution is rapidly diluted in the bloodstream, and the body's buffering system can maintain the proper pH level when high or low pH LVPs are administered, although it does so less easily if the solutions are highly buffered.

Because of its lower cost, type II glass, a flint glass with a surface treatment, is used for many LVPs that are packaged in glass. Solutions with pH values approaching or over 7.0 accelerate glass attack and must be packaged in the more expensive type I borosilicate glass. Since this glass is resistant to attack by alkaline solutions, it is used to prevent the pH from rising even higher. Other problems associated with degradation of the glass surface, such as the formation of glass flakes in the product, can be avoided by the use of type I glass. Chapter 11 provides a thorough discussion of glass containers that are used for packaging parenterals.

**Vehicles** WFI is the vehicle used for all LVPs. All ingredients are dissolved, and the resulting aqueous solution is clear and generally colorless. The IV fat emulsion, an LVP that may be administered alone or in combination with amino acid and dextrose solutions for total parenteral nutrition (TPN) therapy, is the exception. Triglycerides, egg phospholipids, glycerin, and WFI are homogenized to produce a stable emulsion with fat particles approximately 0.3  $\mu\text{m}$  in size.

#### *Physical Parameters*

The sensitivity of a solution when exposed to light and extremes in temperature must be evaluated during the development of a formulation. Certain vitamin solutions require protection from light, for example, in the form of an amber bottle or an opaque unit carton. A light protective cover must be put over containers of solutions to which photodegradable drugs have been added. Solutions with high concentrations of dextrose or combinations with dextrose that have a tendency to develop slight discoloration with age will do so more rapidly if stored at high temperatures. The physical parameters that are defined for a solution are stated on the labeling and packaging inserts.

#### *Packaging Parameters*

The chapters on containers and closures in this textbook provide detailed information about the characteristics of materials available for packaging parenteral medications.

#### *Stabilization of LVPs*

**Added substances.** Buffering agents, chelating agents, antimicrobial preservatives, and antioxidants, commonly added to parenteral medications, are rarely used in LVPs. Buffering agents generally are not added as such, although acids and bases, which are used to adjust pH, can raise or lower the buffering capacity of the solution. By their nature and use, LVPs introduce large amounts of fluid and chemicals into the body. The active ingredients are present for a therapeutic effect, and although present in only very low percentages, added substances might, in total, have an effect on the patient who receives many bottles of solution during the course of treatment.

Very minute quantities of metals such as iron, copper, or calcium may be introduced into LVPs because of ingredients used and hence the quality of the incoming raw materials must be ensured. When drugs are administered orally, the gastrointestinal tract prevents aluminum from being absorbed into patient tissues; however, when the drugs are administered parenterally the aluminum can be deposited in tissues, potentially at toxic amounts. Therefore, according to the latest FDA guideline, the aluminum content of LVP drug products used in TPN therapy must not exceed 25  $\mu\text{g/L}$  (173).

Antioxidants such as sodium bisulfite or sodium metabisulfite are part of some LVP formulations. They are added to protect the active ingredients from the action of oxygen in the solution or headspace of the container. The presence of oxygen, even very small amounts, can accelerate color formation or degradation of such products as 5% Dextrose in lactated ringer's or amino acid solutions. In lieu of the addition of an antioxidant, which might be added in concentrations of up to 0.1%, processing to displace the oxygen with an inert gas, usually nitrogen, may be done during mixing and filling operations. If both nitrogen and an antioxidant are used, the use of nitrogen will reduce the amount of bisulfite needed to protect the product during its shelf life.

#### *Electrolytes, Carbohydrates, and Nutritional*

Typical examples of LVP formulations are shown in Tables 21 to 23. They are only a few of the many formula variations that represent the basic theme of each grouping.

**Electrolyte solutions.** The multiple electrolyte injection is an example of a solution that must be packaged in type I glass or plastic because its high pH, 7.3, can chemically attack type II

**Table 21** Typical Examples of Electrolyte Solutions

Electrolyte	Plasma Lyte R <sup>®</sup>	Isolyte S pH 7.4 <sup>®</sup>	Normosol R <sup>®</sup>
Na <sup>+</sup>	140	141	140
K <sup>+</sup>	10	5	5
Ca <sup>++</sup>	5		
Mg <sup>++</sup>	3	3	3
Cl	103	98	98
Lactate	8		
Acetate	47	27	27
Gluconate		23	23
Phosphate		1	
Osmolarity (mOsm/L)	312	295	294
pH	5.5	7.4	6.6

Source: From Ref. 45.

**Table 22** Examples of Carbohydrate Solutions

Dextrose concentration		Caloric content	Osmolarity
%	g/L	(cal/L)	(mOsm/L)
2.5	25	85	126
5	50	170	253
10	100	340	505
20	200	680	1010
25	250	850	1330
30	300	1020	1515
40	400	1360	2020
50	500	1700	2525
60	600	2040	3030
70	700	2380	3535

Source: From Ref. 45.

**Table 23** Examples of Nutritional Solutions

Solution	Amino acids with electrolytes	Intralipid <sup>®</sup> 10%
mOsm/L	357 1300	260
cal/L		1100
Total nitrogen (g/100 mL)	0.55 2.3	
Formulation	May contain up to 8 essential and 11 nonessential amino acids and electrolytes (Na <sup>+</sup> , K <sup>+</sup> , Cl acetate, and phosphate)	10% soybean oil 1.2% egg yolk phospholipids 2.25% glycerin
Electrolytes		
Antioxidant	May be present	No
Buffering capacity	Moderate	Low
Light Protection	Yes	Yes
Container	Glass, plastic	Glass, plastic

Source: From Ref. 45.

glass surfaces. Each 100 mL of lactated ringer’s injection contains 0.60 g sodium chloride, 0.03 g potassium chloride, 0.02 g calcium chloride, and 0.31 g sodium lactate (anhydrous) in WFI. The lactate ion in this solution is metabolized in the liver to glycogen, which becomes carbon dioxide and water, requiring the consumption of hydrogen ions; the result is an alkalinizing

Downloaded from informahealthcare.com by McGill University on 01/15/13  
For personal use only

effect. Again, the addition of dextrose, 5.0 g/100 mL, is for the caloric value and results in lower pH and higher osmolarity.

Electrolyte solutions make it possible to maintain or, in the case of specific clinical disorders, bring about the balanced levels of water and electrolytes required for proper body functioning.

**Carbohydrate solutions.** A standard solution that provides a source of water for hydration and carbohydrate calories contains Dextrose as a energy substance (Table 22). The dextrose is metabolized rapidly, and the water moves into other body compartments. If it is necessary to replace large losses of body water the injection can be administered, the patient's condition permitting, at a rate as high as 8 10 mL/min. Higher concentrations of the dextrose injection provide more calories without overloading the body with water.

**Nutritional solutions.** For proper nutrition an individual must have an intake of carbohydrates, amino acids, and fatty acids, along with trace minerals and vitamins. Carbohydrate and amino acid solutions have been available as injections for a number of years and can supply part of the patient's nutritional needs. Problems of toxicity, stability of the emulsion, particle size, and formation of free fatty acids had to be overcome before fat emulsions became viable products. Successful commercial production of fat emulsions that could be administered intravenously made it possible to provide the additional calories and essential fatty acids needed to implement TPN for the patient unable to take food enterally.

Fat emulsions typically contain a metabolizable vegetable oil, emulsifying agent, tonicity agent, and WFI. Table 23 shows a formula of fat emulsion in which each 100 mL contains 10 g soybean oil, 1.2 g egg yolk phospholipids as an emulsifying agent, 2.25 g glycerin as tonicity agent, and WFI. Sodium hydroxide is used to adjust the pH to approximately 8.0. In the soybean oil, the major fatty acids are linoleic (50%) and oleic (26%), with palmitic, linolenic, stearic, myristic, arachidic, and behenic acids making up the remainder. Size of the fat particles is controlled to about 0.3  $\mu\text{m}$ . The emulsion is opaque, so the visible signs of incompatibility with additives might be concealed, although breaking of the emulsion results in visible free oil floating on the surface.

Complete amino acid solutions which contain L-amino acids provide the eight essential and as many as ten nonessential amino acids. Studies of blood serum levels of amino acids in normal individuals have established the ranges of each that are present and provide the basis for formulation. Each manufacturer of these solutions has particular combinations of amino acids that have been shown to be effective. There are over 70 amino acid injection formulations now being marketed including specialized amino acid injections (e.g., Aminess<sup>®</sup>, Aminosyn RF<sup>®</sup>, HepatAmine<sup>®</sup>, NephAmine<sup>®</sup>, RenAmin<sup>®</sup>) for patients (e.g., those with renal or hepatic disease) who may have specialized requirements for amino acids or who may not tolerate amino acids contained in conventional solutions (45).

An essential amino acid cannot be converted to another amino acid and must be used by the body to fill a need for that particular one or be converted into uric acid. A nonessential acid may be used if needed, metabolized to another nonessential acid that is needed or converted to uric acid. When amino acids are administered parenterally, adequate calories must be provided concurrently to bring about synthesis of proteins; high-concentration dextrose injection or fat emulsion provides the source of calories. Concentrations of amino acid solutions vary from 3.5% to 15% depending on the indication for use. With some amino acids, however, there are limitations on the amount that will go into solution because the presence of other amino acids has an effect on solubility; the formulation of amino acid solutions is difficult because of this interaction and changing behavior.

#### *Parenteral Nutrition*

It has been estimated that approximately 40 55% of hospitalized patients are malnourished to some degree (174). Nutritional assessment and introduction of parenteral nutrition therapy based on the particular needs of the patient can reverse the nutritional status, minimize the harmful effects of poor nutrition, and accelerate the healing process.

Standard IV therapy usually provides dextrose, water, and electrolytes. Dextrose solutions are available in concentrations of 2.5% to 70%; a 5% solution supplies 170 cal/L and has an osmolality of 280 mOsm/L. These solutions are nutritionally incomplete, cannot supply enough calories without overhydrating the patient, and are suitable only for a few days as a source of nutrition. Electrolytes and vitamins may be added to correct imbalances and ensure normal body functions, including utilization of nutrients.

Amino acid therapy prevents nitrogen loss, is used for treatment of negative nitrogen balance, and provides the building blocks for the protein that is necessary for the return to proper health. These solutions may be given concurrently with oral feeding and, as with any IV solution, provide a route for other medications. They are, like the dextrose solutions, when used alone, nutritionally incomplete and should be given only in the short term to help preserve body protein in a stable patient.

TPN via the central venous route is used for patients with a need for calories and nutrients over a long period of time. High-concentration solutions of dextrose and amino acid solution, for example, 50% dextrose and 8.5% amino acid solution, are admixed in the hospital pharmacy. Trace elements, vitamins, or electrolytes are added to the mixture as needed. This solution will be quite hypertonic, with an osmolality of around 2000 mOsm/L, and must be administered at a carefully controlled rate into a large vein with a high rate of blood flow to achieve proper dilution and minimize irritation of the vein. Infusion is accomplished by inserting a catheter with the tip extending into the superior vena cava and then, via an administration set, connecting the catheter to the bag that contains the admixture. The catheter may remain in place for as long as 30 days with proper care and precautions to avoid sepsis. The 10 or 20% fat emulsion may be administered intermittently through the central vein, through a peripheral vein, or be combined with the dextrose and amino acid solutions in the "mixing bag" prepared in the hospital pharmacy.

#### *Stress Testing*

Stress testing, testing after exposure to exaggerated conditions, is done throughout the developmental process and is designed to establish "safety factors." The data obtained from chemical, microbiological, biological, and physical tests, when compared with the results of tests on samples prepared under normal conditions, provide additional assurance that a safe and effective product will reach the market. Stress testing may take many forms.

Materials that will be in contact with the solution are subjected to extractions that far exceed the normal surface-volume ratios and the extracts are used for chemical, physical, biological, and toxicity testing. Tests for plastic and rubber are listed in various the pharmacopoeias. In addition, the LVP manufacturer may prepare concentrated extracts for tissue culture tests, a screening test for direct cell effects, and tests in rodents and other animals for indications of toxicity. The identity of the material extracted can be established chemically, quantified, and, with the results of the biological tests, related to its effect on humans.

During development of the sterilization cycles, temperature distribution and penetration studies are performed to ensure that the lethality is imparted to the entire sterilizer load. These studies are followed with evaluation lethality of biological indicators in the load. Often, the filled containers are subjected to two or three sterilization cycles and then checked for physical or chemical change.

Product filled containers are tested for drop tests, thermal shock tests, internal pressure tests, and impact resistance. The procedures for these tests are given in manuals that are available from the American Society for Testing Materials (ASTM). Alternating cycles of low and high temperatures provide information about how the solution and container react to adverse storage conditions. Such an evaluation may become part of the initial stability evaluation or the subject of a special stability study.

#### *Stability Evaluation*

Stability evaluation studies are aimed to support expiration dating of the product and also to provide labeling information about shipping and storage conditions, maximum and minimum



temperatures, or the necessity to prevent exposure to light. These studies encompass many aspects: physical (change of color or formation of a precipitate), chemical (change in pH or assay), microbiological (there are no antimicrobial agents in LVPs), or the packaging, which must be nonreactive and protect the solution during the shelf life. For details on the topic of stability studies regarding the stability procedures, sampling requirements, storage conditions, testing schedules, and evaluation of data, reader is directed to chapter 10, volume 3 of this book.

#### *Processing Conditions Affecting Formulation of LVP*

Some aspects of water quality, filtration, and sterilization are described below as they relate to LVP formulation (these have been described in detail in separate chapters elsewhere in this textbook).

WFI is the main ingredient of an LVP formula. Produced in large amounts by distillation or by reverse osmosis, the water must be tested frequently to assure that it is of the quality specified in the compendia. For particulate matter, pharmacopoeias require that each LVP unit must contain no more than 25 particles/mL that are equal to or larger than 10  $\mu\text{m}$  and no more than 3 particles/mL that are equal to or larger than 25  $\mu\text{m}$  in effective linear measurement. Particle generation from any source to which the solution will be exposed must be identified and controlled. Likely sources are air, processing liquids and gases, or components. Each source may contribute only a few particles but in combination can have a significant effect on the quality of the solution. Emphasis should be placed on reducing the generation of particles as well as effective filtration of liquids and gases at the point of use in the process.

LVPs are terminally sterilized, that is, sterilized after the product is filled and sealed in its final container. The sterilization methods generally used is steam under pressure. The type of container, size of container and solution has an effect on the cycle. Plastic containers, for example, are flexible and permeable. Air overpressure inside the sterilizer must be adjusted during the cycle to counteract the internal pressure in the container in order to avoid distortion. The air that prevents distortion also can enrich the oxygen content of the solution and airspace in the container; the result is that 5% dextrose in lactated ringer's develops more color in plastic than in glass. Amino acids are particularly susceptible to oxygen and all but a few are currently packaged in glass. Glass containers are rigid and impermeable but are subject to breakage because of thermal shock if the temperature differentials between the content of the bottle and sterilizer are excessive. The rate of heat up or cooling must be carefully controlled to avoid thermal shock. During sterilization of product in glass containers, the air overpressure in the sterilizer prevents lifting of the closure, which may be brought about by the internal pressure of the bottle. Cycle adjustments must be made for container size; smaller sizes have more surface area available per unit volume than larger sizes and may be used as worst-case samples for studying the effects of heat history.

#### *Admixture Considerations*

Of all LVPs infused, 60% to 80% are estimated to be admixed with one or more drugs (175,176). The number of new drugs and possible combinations is increasing steadily. Appropriate compatibility and stability studies must be performed to ensure that the drugs introduced into LVPs are compatible. The phenomenon of incompatibility occurs when the LVP and drugs produce, by physicochemical means, a product that is unsuitable for administration to the patient. Physical incompatibility may be detected by a change in the appearance of the solution, such as the formation of a precipitate, a haze, a change of color, or the breaking of an emulsion. Subtle incompatibilities, such as a change in pH or drug concentration, may not result in a visual change or may not become evident until a later time.

Instability occurs when an LVP product or admixture is modified because of sorption or such storage conditions as time, light, or temperature. The modified product may not be suitable for administration, and unless the combination has been studied in the laboratory, the only clue to a stability problem may, be failure to get the expected clinical result.

The parameters of tonicity, pH, solubility, and added substances, which were considerations in the design of the LVP formulation, also must be considered in a different context when drugs are added to the solution. The drug product may contain solvents, preservatives, stabilizers, buffers, antioxidants, and other ingredients that, when added to the LVP, can result in instability and incompatibility problems. Sodium benzoate, a preservative in some drugs, precipitates as benzoic acid when added to an LVP with an acidic pH. Copper, a trace metal needed by the body, can cause precipitation in amino acid solutions. Stability of the combination must be maintained after mixing and during infusion if the desired result is to be achieved. Stability problems may be caused by pH, solubility, sensitivity to light or temperature, absorption, or chemical incompatibility. Stability may also be related to time, and this is one reason that it is recommended that admixtures not be stored for prolonged periods.

One example of the role of pH would be that of ampicillin B in dextrose solutions. Unless the pH of the dextrose solution is greater than 5.0, the combination is incompatible. The monograph for Dextrose for Injection allows a pH range of 3.5 to 6.5. When the pH of 5% dextrose in lactated ringer's injection is below 5, some nerve-blocking agents, such as succinylcholine, will precipitate from solution.

Chemotherapeutic drugs and vitamin preparations generally should be protected from light. Sodium bisulfite, an ingredient added to some LVPs to reduce degradation caused by oxidation, may be present in only the quantity needed for protection of the solution during sterilization and shelf life. It may not be present in sufficient quantity to provide protection from the air that may be introduced to the container during admixing or storage in plastic containers.

The order of introduction of drugs to the LVP may either highlight or mask visible incompatibilities. If a drug is incompatible at a given pH and the pH of the LVP must be adjusted, the pH should be adjusted before the drug is added. A fat emulsion, white and opaque, masks reactions that might be visible in a clear solution, and the package insert cautions not to add electrolytes directly to the emulsion.

The potential physical and chemical incompatibilities associated with such dilutions are compiled by Trissel (74) and is often the primary reference book on this subject in the practice of pharmacy.

## REFERENCES

1. The United States Pharmacopeia/The National Formulary (USP 32/NF 27). Rockville: United States Pharmacopeia Convention, Inc., 2009.
2. Strickley RG. Solubilizing excipients in oral and injectable formulations. *Pharm Res* 2004; 2:201-230.
3. Rytting E, Lentz K, Chen X Q, et al. Aqueous and cosolvent solubility data for drug like organic compounds. *AAPS J* 2005; 7:E78-E105.
4. Wohlforth C. Primitivity (DC) of liquids. In: Lide D, ed. *Handbook of Physics and Chemistry*. 88th ed. Boca Raton, Florida: CRC Press, 2007-2008, 6:148-169.
5. Amriyahed AK, Blake MI. Relationship of composition of non aqueous binary solvent systems and dielectric constant. *J Pharm Sci* 1974; 63:81-84.
6. Cave G, Puisieux F, Carstensen J. Dielectric constants of solid liquid and liquid liquid systems as a function of composition. *J Pharm Sci* 1979; 68:424-426.
7. Jouyban A, Soltanpour S, Chan HK. A simple relationship between dielectric constant constant of mixed solvents with solvent composition and temperature. *Int J Pharm* 2004; 269:353-360.
8. Paruta AN. Solubility of the parabens in ethanol water mixtures. *J Pharm Sci* 1969; 58:364-366.
9. Breon TL, Paruta AN. Solubility profiles for several barbiturates in hydroalcoholic mixtures. *J Pharm Sci* 1970; 59:1306-1313.
10. Paruta AN, Mauger JW. Solubility of sodium salicylate in mixed solvent systems. *J Pharm Sci* 1971; 60:432-437.
11. Rubino JT, Yalkowsky SH. Cosolvency and cosolvent polarity. *Pharm Res* 1987; 4:220-230.
12. Hildebrand J, Scott R. The entropy of solution of non electrolytes. *J Chem Phys* 1952; 20:1520-1521.
13. Martin A, Wu PL, Adjei A, et al. Extended Hansen solubility approach: naphthalene in individual solvents. *J Pharm Sci* 1981; 70:1260-1264.
14. Amidon GL, Yalkowsky SH, Leung S. Solubility of non electrolytes in non polar solvents II. Solubility of aliphatic alcohols in water. *J Pharm Sci* 1974; 63:1858-1866.

15. Yalkowsky SH, Amidon GL, Zografi G, et al. Solubility of non electrolytes in polar solvents II. Alkyl p amino benzoates in polar and mixed solvents. *J Pharm Sci* 1975; 64:48 52.
16. Faller B, Ertl P. Computational approaches to determine drug solubility. *Adv Drug Del Rev* 2007; 59:533 545.
17. Jorgensen WL, Durfy EM. Prediction of drug solubility from structure. *Adv Drug Del Rev* 2002; 54:355 366.
18. Gupta P. Solutions and phase equilibria. In: Gennaro A. et al, ed. *Remington the Science and Practice of Pharmacy*. 20th ed. Philadelphia: Lippincott Williams and Wilkins, 2000:208 226.
19. Dai W G, Pollock Dove C, Dong L, et al. Advanced screening assays to rapidly identify solubility enhancing formulations: high throughput, miniaturization and automation. *Adv Drug Del Rev* 2008; 60:657 672.
20. Alsenz J, Kansy M. High throughput solubility measurement in drug discovery and development. *Adv Drug Del Rev* 2007; 59:546 567.
21. Liu R. Water insoluble drug formulation. In: Liu R, ed. Boca Raton, Florida: Interpharm/CRC Press, 2000.
22. Sweetana S, Akers M. Solubility principles and practices for parenteral dosage form development. *PDA J Pharm Sci Tech* 1996; 50:330 342.
23. Guillory J, Pust R. Chemical kinetics and drug stability. In: G. Banker, C. Rhodes, eds. *Modern Pharmaceutics*. New York: Marcel Dekker, 2002:139 165.
24. Bruker M, Stahl PH. Preparation of water soluble compounds through salt formation. In: Wermuth CG, ed. *The Practice of Medicinal Chemistry*. Burlington, MA: Elsevier Science, 2008:747 765.
25. Serajuddin A, Pudipeddi M. Salt selection strategies. In: Stahl PH, Wermuth G, ed. *Handbook of Pharmaceutical Salts: Properties, Selection, and Use*. Weinheim: Wiley VCH, 2002:135 160.
26. Avdeef A. Solubility of sparingly soluble ionizable drugs. *Adv Drug Del Rev* 2007; 59:568 590.
27. Serajuddin A, Sheen P, Augustine M. Common ion effect on solubility and dissolution rate of the sodium salt of an organic acid. *J Pharm Pharmacol* 1986; 587 591.
28. Serajuddin A. Salt formation to improve drug solubility. *Adv Drug Del Rev* 2007; 59:603 616.
29. Hildebrand J. Solubility. XII. Regular solutions. *J Am Chem Soc*, 1929; 51:66 80.
30. Hildebrand J. Solubility. XIV. Experimental tests of a general equation for solubility. *J Am Chem Soc* 1935; (57):866 871.
31. Yalkowsky S, Roseman T. Solubilization of drugs by cosolvents. In: Yalkowsky SH, ed. *Techniques of solubilization of drugs*. New York: Marcel Dekker, 1981:91 134.
32. Martin A, Paruta AN, Adjei A. Extended Hildebrand solubility approach. Methoxyxanthenes in mixed solvents. *J Pharm Sci* 1981; 70:1115 1120.
33. Khoubnasabjafari M, Jouyban A, Acree WE Jr. Mathematical representation of solubility of electrolytes in binary solvent mixtures using Jouyban Acree model. *Chem Pharm Bull* 2005; 53:1591 1593.
34. Jouyban A. Solubility prediction of drugs in water polyethylene glycol 400 mixtures using Jouyban acree model. *Chem Pharm Bull* 2006; 54:1561 1566.
35. Jouyban A. Review of the cosolvency models for predicting solubility of drugs in water cosolvent mixtures. *J Pharm Pharmaceut Sci* 2008; 11:32 58.
36. Yalkowsky S, Flynn G, Amidon G. Solubility of nonelectrolytes in polar solvents. *J Pharm Sci* 1972; 61:983 984.
37. Millard J, Alvarez Nunez F, Yalkowsky SH. Solubilization by Co solvents. Establishing useful constants for the log linear model. *Int J Pharm* 2002; 245:153 166.
38. Rubino JT, Blanchard J, Yalkowsky SH. Solubilization by co solvents IV: benzocaine, diazepam, and phenytoin in aprotic co solvent water mixtures. *J Parent Sci Tech* 1987; 41:172 176.
39. Yalkowsky SH, Davis E, Clark T. Stabilization of aspartame by polyethylene glycol 400. *J Pharm Sci* 1993; 82:978.
40. Connors K, Amidon G, Stella V. *Chemical Stability of Pharmaceuticals: a Handbook for Pharmacists*. 2nd ed. New York: Wiley, 1986.
41. Ni N, Sanghvi T, Yalkowsky S. Stabilization and preformulation of anticancer drug SarCNU. *Int J Pharm* 2002; 249:257 264.
42. Zhao L, Yalkowsky HS. Stabilization of epitibatide by co solvents. *Int J Pharm* 2001; 218:43 56.
43. Trivedi J, Porter W, Fort J. Solubility and stability characterization of Zileuton in a ternary solvent system. *Euro J Pharm Sci* 1996; 4:109 116.
44. PDR<sup>®</sup> Electronic Library also contains Stedman's Medical Dictionary. Stedman's Medical Dictionary is © 2000 2008. Lippincott, Williams & Wilkins.
45. *Facts & Comparisons*<sup>®</sup> 4.0. Indianapolis, IN 46240 USA: Wolters Kluwer Health, Inc., 2009.
46. Schott H. Colloidal dispersions. In: Gennaro A, ed. *Remington the Science and Practice of Pharmacy*. 20th ed. Philadelphia: Lippincott Williams and Wilkins, 2000:288 315.

47. Lawrence ASC. Internal solubility in soap micelles. *Trans Faraday Soc* 1937; 33:815 820.
48. Samaha MW, Naggar VF. Micellar properties of non ionic surfactants in relation to their solubility parameters. *Int J Pharm* 1988; 42:1 9.
49. Akbuga J, Gursoy A. The effect of surfactant on the solubility of tablet dissolution of furosemide. *Sci Tech et Prat Pharm* 1987; 3(5):395 399.
50. Wan L, Philip F. CMC of Polysorbates. *J Pharm Sci* 1963; 63(1):136 137.
51. Liu R, Sadrzadeh N, Constantinides P. Micellization and drug solubility enhancement. In: Liu R, ed. *Water Insoluble Drug Formulation*. Boca Raton, Florida: Interpharm/CRC, 2000:213 277.
52. Abdel Rahman A, Aboutaleb A, Samy E. Factors affecting chlordiazepoxide solubilization. *Bull Pharm Sci Assiut Univ* 1991; 14:35 45.
53. Atwood D, Florence A. *Surfactant Systems: Their Chemistry, Pharmacy, and Biology*. New York: Chapman and Hall, 1983.
54. De Castro B, Gameiro P, Lima J, et al. Acid/base properties of  $\beta$  blockers and benzodiazepines in sodium dodecylbenzoate micelles. A spectrophotometric and potentiometric study. *J Pharm Sci* 1998; 87:356 359.
55. Goto A, Sakura R, Endo F. Effects of sodium chloride on micellar sodium lauryl sulfate solutions solubilizing alkyl parabens. *Chem Pharm Bull* 1980; 28:14 22.
56. Shihab F, Ebian A, Mustafa R. Effect of polyethylene glycol, sodium lauryl sulfate and polysorbate 80 on the solubility of furosemide. *Int J Pharmaceut* 1979; 4:13 20.
57. Uekama K. Pharmaceutical application of cyclodextrins as multi functional drug carriers. *Yakugaku Zasshi*. 2004; 124:909 935.
58. Brewster M, Loftsson T. Cyclodextrins as pharmaceutical solubilizers. *Adv Drug Del Reviews* 2007; 59:645 666.
59. Thompson D. Cyclodextrins enabling excipients: their present and future use in pharmaceuticals. *Crit Rev Therap Drug Carr Syst* 14; 1997:1 104.
60. Stella V, Rajewski R. Cyclodextrins: their future in drug formulation and delivery. *Pharm Res* 14; 1997:556 567.
61. Brewster M, Simpkins J, Hora M, et al. The potential use of cyclodextrins in parenteral formulations. *J Parenter Sci Technol* 1989; 43:231 240.
62. Brewster M, Estes K, Bodor N. Development of a non surfactant formulation for alfaxalone through the use of chemically modified cyclodextrins. *J Parenter Sci Technol* 1989; 43:262 vv.
63. Abilify<sup>®</sup> Prescribing information. Tokyo: Otsuka Pharmaceutical Co., Pvt. Ltd., 2008.
64. Geodon<sup>®</sup> Prescribing information. New York: Pfizer Inc., 2008.
65. Vfend<sup>®</sup> Prescribing information. New York: Pfizer Inc., 2008.
66. Sporanox<sup>®</sup> Prescribing information. Janssen Pharmaceuticals, 2004.
67. Dreyfuss J, Shaw J, Ross Jr. J. Fluphenazine enanthate and fluphenazine decanoate: intramuscular injection and esterification as requirements for slow release characteristics in dogs. *J Pharm Sci* 1976; 65:1310 1315.
68. Nema S, Washkuhn R, Brendel R. Excipients and their use in injectable products. *PDA J Pharm Sci Tech* 1997; 51:166 171.
69. Powell M, Nguyen T, Baloian L. Compendium of excipients for parenteral formulations. *PDA J Pharm Sci Tech* 1998; 52:238 311.
70. Strickley R. Parenteral formulations of small molecules therapeutics marketed in the United States. Part I. *PDA J Pharm Sci Techn* 1999; 53:324 349.
71. Strickley R. Parenteral formulations of small molecules therapeutics marketed in the United States. Part II. *PDA J Pharm Sci Tech* 2000; 54:69 96.
72. Strickley R. Parenteral formulations of small molecules therapeutics marketed in the United States. Part III. *PDA J Pharm Sci Tech* 2000; 54:152 169.
73. Akers M. Excipient drug interactions in parenteral formulation. *J Pharm Sci* 2002; 91:2283 2300.
74. Trissel L. In: Trissel, ed. *Handbook on Injectable Drugs*. Bethesda: American Society of Health System Pharmacists, 1992.
75. Flynn G. J. Buffers pH control within pharmaceutical systems. *Parenter Drug Asso* 1980; 34:139 162.
76. Nema S, Brendel R, Washkuhn R. Excipients their role in parenteral dosage forms. In: Swarbrick J, Boylan J, eds. *Encyclopedia of Pharmaceutical Technology*. Vol. 2. New York: Marcel Dekker, 2002:1164 1187.
77. Schwartz M, Buckwalter F. Pharmaceutics of penicillin. *J Pharm Sci* 1962; 51:1119 1128.
78. Windheuser J, Higuchi T. Kinetics of thiamine hydrolysis. *J Pharm Sci* 1962; 51:354 364.
79. Schwartz M, Granatek A, Buckwalter F. Stability of potassium phenethicillin. *J Pharm Sci* 1962; 51:523 516.

80. Ahmad I, Fasihullah Q, Vaid F. Effect of phosphate buffer on photodegradation reactions of riboflavin in aqueous solution. *J Photochem Photobio* 2005; 78:229 234.
81. Schell G. Relationship between oxidation and pH. *Farm Rev* 1959; 58:45.
82. Yeh S, Lach J. Stability of Morphine in aqueous solution III. Kinetics of Morphine degradation in aqueous solution. *J Pharm Sci* 1961; 50:35 42.
83. Schroeter L. Sulfurous acid salts as pharmaceutical antioxidants. *J Pharm Sci* 1961; 50:891 901.
84. Schroeter L. Kinetics of air oxidation of Sulfurous acid salts. *J Pharm Sci* 1963; 52:559 563.
85. Riegelman S, Fischer E. Stabilization of Epinephrine against sulfite attack. *J Pharm Sci* 1962; 51:206 210.
86. Yousef R, Elnakib M, Salama S. Effect of some pharmaceutical materials on the bactericidal activities of parabens. *Can J Pharm Sci* 1973; 8:54 60.
87. Asker A, Habib M. Photostabilization of menadione sodium bisulfite by glutathione. *J Parenter Sci Tech* 1989; 43:204 207.
88. Smolinske S. Review of parenteral sulfite reactions. *J Tox. Clin Tox* 1992; 30:597 606.
89. Kasraian K, Kuzniar A, Wilson G, et al. Developing an injectable formula containing an oxygen sensitive drug: case study of danofloxacin injectable. *Pharm Dev Technol* 1999; 4:475 480.
90. Meyer B, Ni A, Hu B. et al. Antimicrobial preservative use in parenteral products: past and present. *J Pharm Sci* 2007; 96:3155 3167.
91. Rowe R, Shesky P, Owen S. eds. *Handbook of Pharmaceutical Excipients*. Electronic ed. London Chicago: Pharmaceutical Press, American Pharmaceutical Association, 2005.
92. Smolinske S. In: Smolinske S, ed. *Benzyl Alcohol: Handbook of Food, Drug, Cosmetic Excipients*. Denver: CRC Press, 1992:47 54.
93. Haag T, Loncrini D. Esters of parahydroxybenzoic acid. In: Kabara JJ, ed. *Cosmetic Drug Preservation*. New York: Marcel Dekker, 1984:63 77.
94. Richards R, McBride R. Phenyl ethanol enhancement of preservative used in ophthalmic preparations. *J Pharm Pharmacol* 1971; 23:141S 146S.
95. Kakimi K, Sezaki H, Arakava E, et al. Interactions of parabens and other adjuvants with plastic containers. *Chem Pharm Bull* 1971; 19:2523 2529.
96. Patel N, Kostenbauder H. Interactions of preservatives with macromolecules. I. binding of parahydroxybenzoic acid esters by polyoxyethylene 20 sorbitan monooleate. *J Am Pharm Assoc* 1958; 47:289 293.
97. Aoki M, Kameta A, Yoshioka I, et al. Application of surface active agents to pharmaceutical preparations. I. effect of Tween 20 upon the antifungal activities of p hydroxybenzoic acid esters in solubilized preparations (in Japanese). *J Pharm Soc Jpn* 1956; 76:939 943.
98. Lachman L, Sheth P, Urbanyi T. Lined and unlined rubber stoppers for multiple dose vial solutions I. Sorption of preservatives and leaching of extractives. *J Pharm Sci* 1964; 53:211 218.
99. Lachman L, Weinstein S, Hopkins G, et al. Stability of antibacterial preservative in parenteral solutions I. Factors influencing the loss of antimicrobial agents from solutions in rubber stoppered containers. *J Pharm Sci* 1962; 51:224 232.
100. Martin A, Bustamante P, Chun A. Buffered and isotonic solutions. In: Martin A, ed. *Physical Pharmacy: Physical Chemical Principles in the Pharmaceutical Sciences*. Philadelphia: Lea Febiger, 1993:169 189.
101. Goyan F, Enright J, Wells J. Critical graphical methods for calculating isotonic concentrations and freezing points of aqueous solutions. *J Am Pharm Asso Sci* 1944; 33:74 80.
102. Boylan J, Robison R. Rheological stability of Procaine penicillin suspension. *J Pharm Sci* 1968; 57:1796 1797.
103. Akers M, Fites A, Robison R. Formulation design and development of parenteral suspensions. *PDA J Parenter Sci Tech* 1987; 41:88 96.
104. Davis S, Washington C, West P. Lipid emulsions as drug delivery systems. *Ann NY Acad Sci* 1987; 507:75 88.
105. Gupta P, Cannon J. Emulsions and microemulsions for drug solubilization and delivery. In: Liu Y, ed. *Water Insoluble Drug Formulation*. Boca Raton, Florida: Interpharm/CRC, 2000:169 211.
106. Collins Gold L, Lyons R, Bartholow L. Parenteral emulsions for drug delivery. *Adv Drug Del Rev* 1990; 5:189 208.
107. Burnham W, Hansrani P, Knott C, et al. Stability of a fat emulsion based intravenous feeding mixture. *Int J Pharm* 1983; 13:9 22.
108. Washington C, Connolly M, Manning R, et al. The electrokinetic properties of phodpholipid stabilized fat emulsions. V. The effect of amino acids on emulsion stability. *Int J Pharm* 1991; 77:57 63.
109. Liu R, Cannon J, Li Y. Liposomes in solubilization. In: Liu Y, ed. *Water Insoluble Drug Formulation*. Boca Raton, Florida: Interpharm/CRC, 2000:355 404.

110. Hwang K. Liposome pharmacokinetics. In: Ostro M, ed. Liposome: from Biophysics to Therapeutics. New York: Marcel Dekker, 1987:109 156.
111. AmBisome<sup>®</sup> Prescribing information. San Dimas: Gilead Sciences, Inc., 2000.
112. Doxil<sup>®</sup> Prescribing information. Ortho Biotech Products, 2008.
113. Patravale V, Date A, Kulkarni R. Nanosuspensions: a promising drug delivery system. *J Pharm Pharmaco* 2004; 56:827 840.
114. Muller R, Jacobs C, Kayser O. Nanosuspensions as particulate drug formulations in therapy. Rationale for development and what we can expect for the future. *Adv Drug Del Rev* 2001; 47:3 19.
115. Muller R, Peters K. Nanosuspensions for the formulation of poorly soluble drugs I. Preparation by size reduction technique. *Int J Pharm* 1998; 160:229 237.
116. Merisko Liversidge E, Liversidge G, Cooper E. Nanosizing: a formulation approach for poorly water soluble compounds. *Eur J Pharm Sci* 2003; 18:113 120.
117. Chaubal M, Doty M, Kipp J. et al. Novel process for the preparation of injectable nanosuspension to address insolubility challenges. *Proceedings of the Control Release Society Meeting*, 2003:30.
118. Pace S, Pace G, Parikh I, et al. Novel injectable formulations of insoluble drugs. *Pharm Tech* 1999; 116 133.
119. Muller R, Peters K, Becker K, et al. Nanosuspension for the IV administration of poorly soluble drugs stability during sterilization and long term storage. *22nd Int Symp Control Release Bioact Mater* 1995; Seattle:574 575.
120. Buchmann S, Fischli W, Thiel W, et al. Aqueous nanosuspension, an alternative intravenous formulation for animal studies. *42nd Annual Congress APV, Mainz, Germany*, 1996:124.
121. Merisko Liversidge E, Sarpotdar E, Cruno P et al. Formulation and antitumor evaluation of nanocrystalline suspension of poorly soluble anticancer drugs. *Pharm Res* 1996; 13:272 278.
122. Wong J, Brugger A, Khare A, et al. Suspensions for intravenous (IV) injection: a review of development, preclinical and clinical aspect. *Adv Drug Del Rev* 2008; 60:939 954.
123. Nyman D, Campbell K, Hersh E, et al. Phase I and pharmacokinetics trial of ABI 007, a novel nanoparticle formulation of paclitaxel in patients with advanced nonhematological malignancies. *J Clin Oncol* 2005; 1:7785 7793.
124. Olavarria E, Hassan M, Eades A, et al. A phase I/II study of multiple dose intravenous busulfan as myeloablation prior to stem cell implantation. *Leukemia* 2000; 14:1954 1959.
125. DeLuca, P, Lachman L. Lyophilization of pharmaceuticals. I. Effect of certain physical chemical properties. *J Pharm Sci* 1965; 54:617 624.
126. Lachman L, DeLuca P, Withnell R. Lyophilization of pharmaceuticals. II. High sensitivity resistance bridge for low conductivity measurements at eutectic temperatures. *J Pharm Sci* 1965; 54:1342 1347.
127. Pikal M. Freeze drying of proteins part II: formulation selection. *BioPharm* 1990; 3:26 30.
128. IMS Healthcare Incorporated. Subscription Data, 2008.
129. Cameron P, ed. *Good Pharmaceutical Freeze Drying Practice*. Buffalo Grove: Interpharm Press, 1997.
130. Franks F. Freeze Drying of bioproducts: putting principles into practice. *Eur J Pharm Biopharm* 1998; 45:221 229.
131. Jennings T. *Lyophilization Introduction and Basic Principles*. Denver: Interpharm Press, 1998.
132. Nail S, Gatlin G. Freeze drying: principles and practice. In: Avis KE, Lieberman HA, Lachman L, eds. *Pharmaceutical Dosage Forms: Parenteral Medications*. Vol. 2. New York: Marcel Dekker, Inc., 1992:163 233.
133. Tang X and Pikal P. Design of freeze drying processes for pharmaceuticals: practical advice. *Pharm Res* 2004; 21:191 200.
134. Kamat M, Koida Y, DeLuca P. Novel method to lyophilize aqueous solutions of lactose and sucrose. Presented at the annual conference of American Association of Pharmaceutical Scientists. Orlando, 1988.
135. Kasraian K, DeLuca P. Thermal analysis of the tertiary butyl alcohol water system and its implications in freeze drying. *Pharm Res* 1995; 12:484 490.
136. Pikal M, Roy M, Shah S. Mass and heat transfer in vial freeze drying of pharmaceuticals: role of the vial. *J Pharm Sci* 1984; 73:1224 1237.
137. Liapis A, Bruttini R. A Theory for the primary and secondary drying stages of the freeze drying of pharmaceutical crystalline and amorphous solutes: comparison between Experimental data and theory. *Sep Technol* 1994; 4:144 155.
138. Liapis A, Bruttini R. Freeze drying of pharmaceutical crystalline and amorphous solutes in vials: dynamic multi dimensional models of the primary and secondary drying stages and qualitative features of the moving interface. *Drying Technol* 1995; 13:43 72.
139. Liapis A, Pikal M, Bruttini R. Research and development needs and opportunities in freeze drying. *Drying Technol* 1996; 14:1265 1300.

140. Rambhatla S, Obert J, Luthra S, et al. Cake shrinkage during freeze drying: a combined experimental and theoretical study. *Pharm Dev Techn* 2005; 1:33 40.
141. Rowe RC, Wakerly MG, Roberts RJ, et al. Expert systems for parenteral development. *J Pharm Sci Tech* 1995; 49:257 262.
142. Ku S H, Cadwallder D. Behaviour of erythrocytes in ternary solvent systems. *J Pharm Sci* 1975; 64:1818 1821.
143. Fort F, Heyman I, Keterson J. Hemolysis study of aqueous polyethylene glycon 400, propylene glycol and ethanol combinations in vivo and in vitro. *J Parent Sci Technol* 1984; 38:82 87.
144. Johnson J, He, Y, Yalkowsky S. Prediction of precipitation induced phlebitis: a statistical validation of an in vitro model. *J Pharm Sci* 1999; 92:1574 1581.
145. Schroeder H, DeLuca P. A study on the in vitro precipitation of poorly soluble drugs from nonaqueous vehicles in human plasma. *Bull Parenteral drug Ass* 1974; 28:1 14.
146. Ward G, Nolan Jr. P, White, M, et al. Studies in phlebitis. II. Early detection of amiodarone induced phlebitis in a rabbit model. *Pharm Res* 1991; 8:801 803.
147. Simamora P, Pinsuwan S, Alvarez J, et al. Effect of pH on injection phlebitis. *J Pharm Sci* 1995; 84:520 522.
148. Ward G, Yalkowsky S. Studies in phlebitis V: hemolysis as a model for phlebitis. *J Parenteral Sci Tech* 1993; 47:44 46.
149. Maerlin G, Thompson P, Jenkins C, et al. Study of serum levels, venous irritations, and gastro intestinal side effects with intravenous erythromycin lactobionate in patients with broncho pulmonary infection. *Human Toxicol* 1983; 2:593 605.
150. Klement W, Arndt J. Pain on injection of Propofol: effects of concentration and diluents. *Br J Anesth* 1991; 67:281 284.
151. Yalkowsky S, Krzyzaniak J, Ward G. Formulation related problems associated with intravenous drug delivery. *J Pharm Sci* 1998; 87:787 796.
152. Li P, Vishnuvajjala R, Tabibi S, et al. Evaluation of in vitro precipitation methods. *J Pharm Sci* 1998; 87:196 199.
153. Gray J. Appraisal of the intramuscular irritation test in rabbits. *Fund Appl Toxicol* 1981; 1:290 292.
154. Gupta P, Patel J, Hahn K. Evaluation of pain and irritation following local administration of parenteral formulations using rat paw lick model. *PDA J Pharm Sci Technol* 1994; 48:159 166.
155. Trissel L. Compatibility issues in parenteral administration (panel discussion presentation). *PDA J Pharm Sci Tech* 1995; 309 313.
156. International Conference on Harmonization. Q8. Pharmaceutical development, EMEA/CHMP/167068/2004 ICHH, May 2006, CH8.
157. Moldenhauer J. Determining whether a product is steam sterilizable. *PDA J Pharm Sci Tech* 1996; 50:28 35.
158. Morris J. Sterilisation decision trees development and implementation. *PDA J Pharm Sci Tech* 2000; 54:1 4.
159. de Vries H, van Henegouwen B, Huf F. Photochemical decomposition of chloramphenicol in a 0.25% eyedrop and in a therapeutic intraocular concentration. *Int J Pharm* 1984; 20:265 271.
160. Asker A, Colbert D. Influence of certain additives on the photostabilizing effect of uric acid for solutions of FD and C blue no.2. *Drug Dev Ind Pharm* 1982; 8:759 774.
161. Asker A, Harris C. Influence of certain additives on the photostability of physostigmine sulfate solutions. *Drug Dev Ind Pharm* 1988; 14:733 746.
162. Asker A, Habib M. Effect of certain additives on photodegradation of tetracycline hydrochloride solutions. *J Parent Sci Tech* 1991; 45:113 115.
163. Asker A., Islam M. Effect of sodium thiosulphate on the photolysis of phenobarbital: evidence of complex formation. *PDA J Pharm Sci Tech* 1994; 48:205 210.
164. Tonnenson H. Formulation and stability testing of photolabile drugs. *Int J Pharm* 2001; 225:1 14.
165. Guideline International Conference on Harmonization. Q1B, 1997a. Photostability testing of new drug substances and products. *Federal Register* 1997; 62:27115 27122.
166. Moore D. Photophysical and photochemical aspects of drug stability. In: Tonnesen HH, ed. *Photostability of Drugs and Drug Formulations*. London: Tylor & Francis, 1996:9 38.
167. Thoma K, Kunbler N. Einfluss der Wellenlaenge auf die Photozersetzung von Arzneistoffen. *Pharmazie* 1996; 51:660 664.
168. Wollmann H, Grunnert R. Einfluss des sichtbaren Lichtes auf die Haltbarkeit von Isoprenalin, Epinephrin und Levaterenollosungen in unterschiedlichen Behaeltnissen. *Pharmazie* 1984; 39: 161 163.
169. Epidemiological notes and reports Nosocomial bacteremias associated with intravenous fluid therapy. *MMWR* 1997; 46(51):1227 1233.

170. Miller M. Principles of IV medication administrations. In: Nentwich PA, ed. *Intravenous Therapy*. Boston, MA: Jones and Bartlett Publishers, 1990; 69-84.
171. Gahart B, Nazareno A. *Intravenous Medications: a Handbook for Nurses and Health Professionals*. 25th ed. Mosby Elsevier, 2009.
172. Buxton I. "Chapter 1. Pharmacokinetics and pharmacodynamics: the dynamics of drug absorption, distribution, action, and elimination" (chapter). In: Brunton LL, Lazo JS, Parker KL, eds. *Goodman & Gilman's the Pharmacological Basis of Therapeutics*. 11th ed. Available at: <http://www.accessmedicine.com/content.aspx?aID=935800>.
173. Aluminum in large and small volume parenterals used in total parenteral nutrition. Code of Federal Regulations. Volume 4, 21CFR201.323.5, 2008.
174. Gallagher Allerd C, Voss A, Finn S, et al. Malnutrition and clinical outcomes: the case for medical nutrition therapy. *J Am Diet Assoc* 1996; 96:361-369.
175. Weinstein S. *Plummer's Principles and Practice of Intravenous Therapy*. Lippincott William and Wilkins, 2006.
176. Trissel L. Drug stability and compatibility issues in drug delivery. *Cancer Bull* 1990; 42:393-398.



## 6 | Drug solubility and solubilization

Ching-Chiang Su, Lan Xiao, and Michael Hageman

### SOLUBILITY AND PARENTERAL PRODUCTS

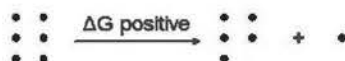
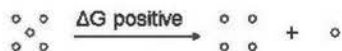
This chapter provides a practical description of the physical phenomena leading to molecular level solubilization or dispersion of solutes (drugs) in a way that should enable the formulator to make informed decisions regarding formulation strategies for parenteral delivery. Solubility is discussed from the perspective of a thermodynamically defined equilibrium requiring several energetic steps in going from solute in a condensed phase to a solute in solution. Discussions will include the nonequilibrium state of supersaturation while focusing on the fit-for-purpose definition of solubility targeting parenteral drug delivery. The definition of solubility can relate to the solubility of any physical state of matter in another, or even in a similar state (miscibility), but this chapter will focus on solubility of a solid state in a liquid media, resulting in a solution mixture, which is of primary pharmaceutical importance for parenteral drug delivery (1).

Thermodynamic solubility can be described as the condition where the chemical potential of solute ( $\mu_{\text{solute}}$ ) in solution is in equilibrium with, and equal to, the chemical potential of the solute in its respective solid phase ( $\mu_{\text{solid}}$ ) under consideration (2). At a constant temperature and pressure, this equilibrium defines the saturated solution with respect to the designated solid phase and respective media. Any perturbation in the solute phase or solvent phase can result in a temporary metastable state of either supersaturation ( $\mu_{\text{solute}} > \mu_{\text{solid}}$ ) or subsaturation ( $\mu_{\text{solute}} < \mu_{\text{solid}}$ ), where the chemical potentials differ and the system will spontaneously attempt to reestablish equilibrium. Any effort to intentionally alter solubility will require a modification in the chemical potentials of either the solute solid state or the solute in solution.

To better understand strategies to modify solubility, three key energetic drivers for the solubilization process should be considered (2). The first step is the necessary energy input to overcome the intermolecular interactions of the solute in its respective condensed state (Fig. 1). The second step is the energy input necessary to overcome solvent-solute interactions and create a cavity in the solvent which accommodates the solute. The unfavorable energy input to this point is then countered with the energy release occurring upon collapse of the solvent cavity around the solute and ensuing intermolecular interactions between solute and solvent.

Alterations in the solvent can influence both solvent-solvent interactions and subsequent solvent-solute interactions. This is the basis for many of the cosolvent strategies used for solubilization, wherein the  $\mu_{\text{solute}}$  is decreased shifting the equilibrium toward increased amounts of drug in solution. Solubilization through changes in the solid form of a drug (amorphous, polymorphs, etc.) leads to increases in the  $\mu_{\text{solid}}$ , which also shifts the equilibrium, but also runs the risk of conversion to a more thermodynamically stable and less soluble solid form with time. Solubilization obtained through alterations in the solute's molecular structure has the potential to significantly alter solubility by impacting specific solvent-solute interactions or solute-solute interactions. This is probably the preferred strategy for enhancing solubility, but such molecular modifications are difficult to introduce once the drug development process on an entity has been initiated. Hence, molecular design modifications are best instituted through interactions with medicinal chemists in the discovery organization prior to drug candidate selection.

One of the most commonly used strategies to provide apparent increases in solubility, or total drug in solution, is to create alternative equilibria for the drug or solute to reside in. While these equilibria enhance the total amount of drug in solution, the  $\mu_{\text{solute}}$  remains equivalent to that of the solid phase, that is, the intrinsic solubility is not altered but instead the  $\mu_{\text{solute}}$  residing in some additional equilibrium is reduced through specific interactions or altered solvation. Creation of alternative equilibria to "sequester" drug provides the basis for solubilization strategies, such as micellar partitioning, chemical ionization, complexation, and partitioning into emulsions.

**Step 1. Removal of a molecule from its condensed phase****Step 2. Creating a cavity in the solvent****Step 3. Release of solvation energy****Figure 1** An illustration of the three steps needed for drug solubility.

In the simplest of terms, the solubility of a solute in a given solvent system, as defined by amount of drug dissolved, seems easily determined, but reliable, reproducible and meaningful numbers can be difficult to obtain. The more common methods are best described as “fit for use,” wherein the solid phase of interest is incubated in solvent and the total amount of solute present in solution is measured. The method of solid-phase separation is critical and really defines the utility of the apparent solubility obtained. Typically, either filtration or centrifugation is used with subsequent assay of filtrate (filtration) or supernatant (centrifugation). Details of separation can be particularly important when colloid scale dispersions exist. Furthermore, as solubilities begin to drop below 1  $\mu\text{g}/\text{mL}$ , issues of nonspecific adsorption to surfaces (filter, container), coupled with analytical detection limitations can result in highly variable values across labs.

Factors such as temperature, energy input and the nature of both the solid phase and the solvent can significantly impact how rapidly equilibrium is obtained. Approaching equilibrium from both a state of supersaturation and subsaturation taking measurements as a function of time is probably the best approach. At equilibrium both should approach similar values. When solubilities are  $> 1 \mu\text{g}/\text{mL}$ , 24-hour incubation will generally approach 90% to 95% of equilibrium value, assuming particle sizes are small (3).

**IMPLICATIONS OF SOLUBILITY FOR PARENTERALS**

A common challenge in development of drugs intended for parenteral administration is the solubilization of a poorly soluble active ingredient (4). For intravenous (intravascular) injection, solubility of the active ingredient in the plasma needs to be below saturation upon dilution to prevent precipitation or formation of phlebitis. Injection of a drug into an extravascular site may establish a depot depending on the type of formulation administered. Drug absorption from a depot by passive diffusion and partitioning is dependent on drug solubility. Only the fraction of drug in solution is available for absorption. A critical difference between the pH of the administered drug solution and the physiological pH at the injection site (and/or solubility of the drug in a cosolvent vehicle and in physiological tissue fluid) can cause an unpredicted decrease in absorption due to precipitation of the drug at the injection site. Phenytoin is formulated as a sodium salt in a pH 12 solution of 40% propylene glycol, 10% alcohol and water for injection. When injected into muscle tissue, the large difference in pH and simultaneous dilution of propylene glycol with tissue fluids cause conversion of the sodium salt to less soluble free acid and precipitation at the injection site. Amphotericin B has a low aqueous solubility of 0.1  $\text{mg}/\text{mL}$  at pH 2 or pH 11. However, Amphotericin B is highly soluble in liposomal intercalation and becomes an integral part of the lipid-bilayer membrane. These liposomal products permit administration by IV infusion. Another commonly studied low solubility drug is paclitaxel with an aqueous solubility of 0.1  $\mu\text{g}/\text{mL}$ . Wheeler et al. manufactured an emulsion and liposome blend using corn oil, cholesterol and egg phosphatidylcholine containing 5  $\text{mg}/\text{mL}$  of paclitaxel, a 50,000-fold increase in solubility (5).

### PROPERTIES OF THE SOLVENT

A popular aphorism used for predicting solubility is "like dissolves like" (6). This statement indicates that a solute will dissolve best in a solvent that has a similar polarity to itself. This view is rather simplistic, since it ignores many solvent-solute interactions, but it is a useful rule of thumb. Strongly polar compounds like sugars or ionic compounds like inorganic salts dissolve only in very polar solvents like water, while strongly nonpolar compounds like oils or waxes dissolve only in very nonpolar organic solvents like hexane. The dielectric constant, solubility parameter and interfacial/surface tension are among the most common polarity indices used for solvent blending to improve solubility.

Generally, the dielectric constant of the solvent provides a rough measure of a solvent's polarity. It is the electric permittivity ratio of solvent to vacuum. It measures the solvent's ability to reduce the strength of the electric field surrounding a charged particle immersed in it. This reduction is then compared with the field strength of the charged particle in a vacuum. In general, polar solvents have higher dielectric constant values than nonpolar molecules. Solvents with a dielectric constant of less than 15 are generally considered nonpolar (7). The dielectric constants of some commonly used solvents and cosolvents in parenteral products are listed in (Table 1).

Gorman and Hall (10) studied the solubility of methyl salicylate in isopropanol-water mixtures, and obtained a linear relationship between log mole fraction of the methyl salicylate and the dielectric constant of the mixed solvent.

For a solution to occur, both solute and solvent molecules must overcome their own intermolecular attraction forces, so called van der Waals forces, and find their way between and around each other. This is accomplished best when the attractions between the molecules of both components are similar. The solubility parameters are defined to express the cohesion between like molecules. It is a numerical value that indicates the relative solvency behavior of a specific solvent and can be calculated from heats of vaporization, internal pressures, surface tensions, and other properties, as described by Hildebrand and Scott (11). The heat of vaporization in conjunction with the molar volume of the species, when available at the desired temperature, probably affords the best means for calculating the solubility parameter. It can be expressed as equation (1).

$$\delta = \left( \frac{\Delta H_v}{V_1} - \frac{RT}{V_1} \right)^{1/2} \quad (1)$$

where  $\Delta H_v$  is the heat of vaporization and  $V_1$  is the molar volume of the liquid compound at the desired temperature,  $R$  is the gas constant, and  $T$  is the desired absolute temperature. Hildebrand and Scott include solubility parameters for a number of compounds in their book. A table of solubility parameters has also been compiled by Hansen and Beerbower (12), wherein the authors introduced partial solubility parameters  $\delta_D$ ,  $\delta_P$ , and  $\delta_H$ . The parameter  $\delta_D$  accounts for nonpolar effects,  $\delta_P$  for polar effects, and  $\delta_H$  to express the hydrogen bonding

**Table 1** Dielectric Constant, Solubility Parameter, and Surface Tension of Common Solvents and Cosolvents

Solvent	Dielectric constant	Solubility parameter (cal/cm <sup>3</sup> ) <sup>1/2</sup>	Surface tension 20°C (dyne/cm)
Water	78.5	23.4	72.8
Ethanol	24.3	12.7	22.4
Propylene glycol	32	14.8	38.0
Glycerin	43	16.5	64.3
PEG 300 or 400	35	9.9	43.5 (PEG 200)
Benzyl alcohol	13	12.1	40.7
Dimethyl sulphoxide (DMSO)	47	12.0	43.5
<i>N,N</i> dimethylacetamide (DMA)	38	10.8	36.7
<i>N,N</i> dimethylformamide (DMF)	37	12.1	39.1
<i>N</i> methyl 2 pyrrolidone (NMP)	32	23.0	40.8

Source: From Refs. 8 and 9.

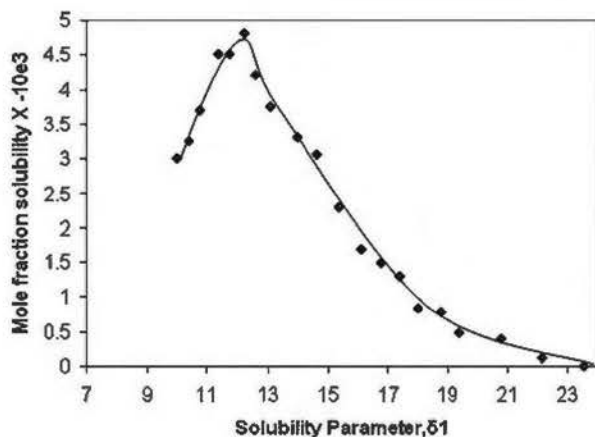


Figure 2 Solubility of trimethoprim in dioxane water mixture of varying solubility parameter. Source: From Ref. 14.

nature of the solvent molecules. The sum of the squares of the partial parameters gives the total cohesive energy density  $\delta_{(\text{total})}^2$  [eq. (2)]. Kesselring et al. have determined both total and partial solubility parameters using gas-liquid chromatography (13).

$$\delta_{(\text{total})}^2 = \delta_D^2 + \delta_P^2 + \delta_H^2 \quad (2)$$

The more alike are the  $\delta$  values of two components, the greater is the mutual solubility, miscibility, of the pair. For example, the  $\delta$  value of phenanthrene is 9.8; it would be expected to be more soluble in carbon disulfide with a  $\delta$  value of 10 than in normal hexane with a  $\delta$  value of 7.3. Conversely,  $\delta$  of a drug can be estimated from measured solubility as a function of solvent solubility parameter (14) (Fig. 2).

Interfacial/surface tension is another solvent property caused by the attraction between the liquid's molecules by various intermolecular forces. It is a measure of the work required to create a cavity of unit area of surface from molecules in the bulk, hence relating to cavity formation for solutes. Polar solvent generally has higher surface tension than nonpolar solvent. Some surface tension and interfacial tension (against water) at 20°C are listed in Table 1 (15).

### PROPERTIES OF THE SOLUTE

Drug molecules contain different structures and functional groups. The collective contributions from each functional group make the macroscopic physicochemical properties of the drug, which are a reflection of inter- or intramolecular interactions. For example, the stronger the attractions between molecules or ions, the more difficult it is to separate the molecules, therefore, the higher the melting point and poorer the solubility. The intra- or intermolecular forces are dictated by intrinsic molecular properties, such as polarizability, electronic factors, topology and steric factors, lipophilicity, hydrogen bonding, surface areas, volumes and connectivity, etc.

#### Molecular Properties

##### *Polarizability and Electronic Factors*

Polarizability is a characteristic property of the particular molecule. It is defined as the ease with which an ion or molecule can be polarized by any external forces. From electromagnetic theory, there is a relationship between polarizability  $\alpha_p$  and dielectric constant  $\epsilon$  of a molecule, where  $n$  is the number of molecules per unit volume [eq. (3)].

$$\frac{\epsilon - 1}{\epsilon + 2} = \frac{4}{3} \pi \cdot n \cdot \alpha_p \quad (3)$$

When a molecule cannot be represented by a single Lewis structure, that is, using an integral number of covalent bonds between two atoms, but rather has properties in some sense

intermediate to these, resonance structures are then employed to approximate the true electronic structure. Because of confusion with the physical meaning of the word resonance, as no elements actually appear to be resonating, it has been suggested that the term resonance be abandoned in favor of delocalization and delocalization energies (16).

An electric dipole is a separation of positive and negative charges. It can be characterized by dipole moment,  $\mu$ , which is equal to the product of charge on the atoms and the distance between the two atoms bounded with each other. Many molecules have such dipole moments because of nonuniform distributions of positive and negative charges on the various atoms. Such is the case with polar compounds like hydroxide ( $\text{OH}^-$ ), where electron density is shared unequally between atoms. Dipole moment is the polarity measurement of a polar covalent bond. The higher the polarity of a molecule the greater the dipole moment and the value can be calculated through the comparison of dielectric constant and the refractive index of the solutions.

Some drugs are known to form a charge-transfer complex with certain solvents. A charge-transfer complex (or CT complex, electron-donor-acceptor-complex) is a chemical association of two or more molecules, or of different parts of one very large molecule, in which the attraction between the molecules (or parts) is created by an electronic transition into an excited electronic state, such that a fraction of electronic charge is transferred between the molecules. The resulting electrostatic attraction provides a stabilizing force for the molecular complex. The association does not constitute a strong covalent bond and is subject to significant temperature, concentration, and host (e.g., solvent) dependencies and occurs in a chemical equilibrium with the independent donor (D) and acceptor (A) molecules.

The great majority of drugs contain ionizable groups; most are basic, some are acidic. The ionization constant ( $K_a$ ) indicates a compound's propensity to ionize. It is a function of the acidity or basicity of group(s) in the molecule. Because of the many orders of magnitude spanned by  $K_a$  values, a logarithmic measure of the constant is more commonly used in practice, wherein the  $\text{p}K_a$  is equal to  $-\log_{10} K_a$ . The equilibria for acids [eqs. (4) and (5)] and for bases [eqs. (6) and (7)] are described as follows:



$$\text{p}K_a = \log\left(\frac{[\text{H}^+] \cdot [\text{A}^-]}{[\text{HA}]}\right) \quad (5)$$



$$\text{p}K_a = \log\left(\frac{[\text{H}^+] \cdot [\text{B}]}{[\text{HB}^+]}\right) \quad (7)$$

Rearranging the  $\text{p}K_a$  equations give the well-known Henderson-Hasselbalch equations for both weak acid (HA) and weak base (B) and the ability to calculate the percentage of ionized species at any particular pH [eqs. (8) and (9)].

$$\text{pH} = \text{p}K_a + \log\left(\frac{[\text{A}^-]}{[\text{HA}]}\right) \quad (8)$$

$$\text{pH} = \text{p}K_a + \log\left(\frac{[\text{B}]}{[\text{BH}^+]}\right) \quad (9)$$

When the pH is two units either side of the  $\text{p}K_a$ , then the drug will be almost completely ionized ( $\text{BH}^+$ ,  $\text{A}^-$ ) or unionized (B, HA). The solution pH and the  $\text{p}K_a$  are important because the charged form of a drug is more soluble than the neutral form. To have any realistic chance of significant pH-solubility manipulation for a parenteral, the  $\text{p}K_a$  for a base must be greater than 3 and for an acid less than 11.

#### *Lipophilicity*

Lipophilicity is the tendency of a compound to partition into a nonpolar lipid matrix versus an aqueous matrix. Lipophilicity is readily calculated, thanks to the work of Hansch and Leo (17).

It is a rapid and effective tool for initial compound property assessment. One traditional approach for assessing lipophilicity is to partition the compound between immiscible nonpolar and polar liquid phases. Traditionally, octanol is the nonpolar phase and aqueous buffer as the polar phase with the partition value,  $\log P$  defined below [eq. (10)].  $\log P$  is measured at a pH of the buffer where all of the compound molecules are in the neutral form.

$$\log P = \log \frac{[C_{\text{nonpolar}}]}{[C_{\text{polar}}]} \quad (10)$$

#### *Hydrogen Bonding*

The assumption that the solubility of a solute in a given solvent is related simply to the bulk properties of the pure components, that is, "like dissolves like," was originally intended strictly for systems involving only London dispersion forces. For quite polar solution components, the specific intermolecular interactions, such as hydrogen bonding, when they occur, are often the dominant factors in determining solubility (18).

A hydrogen bond is a special type of attractive interaction that exists between an electronegative atom and a hydrogen atom covalently bonded to another electronegative atom. Usually the electronegative atom is oxygen, nitrogen, or fluorine, which has a partial negative charge and is the hydrogen bond acceptor. The hydrogen then has the partial positive charge and is the hydrogen bond donor. The typical hydrogen bond is stronger than van der Waals forces, but weaker than covalent or ionic bonds and can occur intermolecularly, or intramolecularly. When hydrogen bonding between solute and solvent is possible, solubility is greater than expected for compounds of similar polarity that cannot form hydrogen bonds. Hansen and Beerbower (12) have introduced hydrogen bond partial solubility parameter,  $\delta_{\text{H}}$ , to account for the nonideality effect from hydrogen bonding on total solubility (see above).

#### *Topology and Steric Factors*

It is believed that the variations in the magnitude of solubility of different solutes in water are caused by their dissimilar chemical structures and much attention has been paid to quantitative structure activity relationship (QSAR) studies of modeling the relationship between chemical structure and solubility of organic compounds. Molecular topology as one of the structure indices has been used widely to study the solubility of compound in different models (18,19).

Molecular topology is the mathematical description of molecular structure allowing a unique and easy characterization of molecules by means of invariants, called topological indices, which are the molecular descriptors to correlate with the experimental properties. Different from the conventional physicochemical descriptors, topological indices (TIs) allow the use of the QSAR relations to design new compounds from scratch. This is possible because, contrary to the physical parameters, the algebraic descriptors are not indirectly related to structure but they are a mathematical depiction of the structure itself.

Besides the chemical structure of the molecules, the spatial arrangement of their functional groups can play a significant role in compound solubility when it influences the degree of interaction between solute and solvent. For example, two isomers can exhibit very different solubilities in the same solvent (20). The influence of the location of the functional groups is referred to here as the steric effect. For strongly interactive solvents like water, the steric effect is particularly severe and sometimes dominating when it hinders or promotes hydrogen bonding interaction. On the other hand, structural alterations that are not in the vicinity of an interacting functional group and do not alter the functionality of the group, have little influence on solubility.

#### *Surface Areas, Volumes, Connectivity*

Theoretically, the dissolution process of a crystalline solid can be carried out in four hypothetical steps: (1) melting of the crystalline solute, (2) separation of a solute molecule from the molten bulk, (3) creation of a cavity in the solvent for accommodation of a solute, and (4) placement of the solute molecule into the cavity created. The energy required for these

processes can be characterized using the enthalpy of melting, the cohesive energy of the solute and solvents, and the adhesive energy at the interface, which are directly proportional to the interfacial area. Hence, solubility can be related to the molecular surface area of a solute.

The solubility in water of aliphatic compounds has been successively related to molecular surface area by Amidon and associates (21,22). They investigated the aqueous solubility of hydrocarbons, alcohols, esters, ketones, esters, and carboxylic acids. Excluding olefins, a linear relationship was found between log (solubility) and total surface area with 158 compounds that they investigated. Similarly, molar volume of the solute is another property impacting solubility. It is related to molecular weight and affects the size of the cavity that must be formed in the solvent to solubilize the molecule.

Molecular connectivity is a measure of extent of molecular branching and normally used as a connectivity index. The connectivity index, easily computed, based on the degree of connectedness at each vertex in the molecular skeleton, is shown to give highly significant correlations with water solubility of branched, cyclic, and straight-chain alcohols and hydrocarbons as well as boiling points of alcohols (23). These correlations are superior to those based on well-founded theory relating to solvent cavity surface area.

### Macroscopic Properties

The melting point or freezing point of a pure crystalline solid is strictly defined as the temperature at which the pure liquid and solid exist in equilibrium. The heat absorbed when a gram of a solid melts, or the heat liberated when it freezes, is known as the latent heat of fusion. The heat added during the melting process does not bring about a change in temperature until the entire solid has disappeared, since this heat is converted into the potential energy of the molecules that have escaped from the solid into the liquid state.

The heat of fusion may be considered as the heat required to increase the interatomic or intermolecular distances in crystals, thus allowing melting to occur. Heat of fusion is dictated by crystal packing. A crystal that is packed by weak forces generally has a low heat of fusion and a low melting point, whereas one packed together with strong forces has a high heat of fusion and a high melting point.

Solubility, as discussed earlier, is strongly influenced by intermolecular forces, similar to melting point. This similarity was demonstrated by Guttman and Higuchi, who studied the melting points and solubilities of xanthenes. When the side chain at 7 position changed from H (theophylline) to propyl (7-propyltheophylline), the melting point decreased from 270 to 100°C, while solubility in water at 30°C increased from 0.045 to 1.04 mol/L. An empirical equation was derived by Yalkowsky and Banerjee (24) to estimate solubility on the basis of the lipophilicity and melting point [eq. (11)].

$$\text{Log}S = 0.8 \log P_{ow} - 0.01(\text{MP} - 25) \quad (11)$$

Here  $S$  is solubility,  $\log P_{ow}$  is the octanol/water partition coefficient (a measure of lipophilicity), and  $\text{MP}$  is the melting point (a measure of crystal packing).

Polymorphs exist when two crystals have the same chemical composition but different unit cell dimensions and crystal packing. Compounds that crystallize as polymorphs generally have different physical and chemical properties, including different melting points, x-ray diffraction patterns, and solubilities. Generally, the most stable polymorph has the highest melting point and lowest solubility; other polymorphs are metastable and convert. A consideration of the data in the literature indicates that improvements in solubility of metastable crystal forms can be expected to be as high as twofold (25).

When the crystal lattice contains solvents that induce polymorphic changes, they are called solvates. If the solvent is water, these pseudo-polymorphs are called hydrates. These hydrates and solvates are easily confused with true polymorphism and lead to the term pseudo-polymorphism. The solvates may be discriminated by DSC/TGA, where an additional endotherm due to the solvent will be apparent in DSC provided the heating rate is slow, and weight loss at similar temperature is observed in TGA.

Hydrate formation generally leads to a lower solubility since the preexistence of water in the crystal lattice reduces the energy available for solvation. For example, glutethimide

anhydrate has melting point 83°C and solubility 0.42mg/mL, but its hydrate has melting point 68°C but solubility only 0.26mg/mL. However, solvates tend to have higher solubility than the neat form because of the weakening of the crystal lattice by the organic solvent. For example, succinylsulphathiazole neat has a solubility of 0.39mg/mL, and its pentanol solvate has solubility of 0.80mg/mL (26).

Amorphous solids may be considered as supercooled liquids in which the molecules are arranged in a random manner somewhat as in the liquid state and do not have melting points. Amorphous solids are in a high energy state relative to their respective crystalline solids, therefore, leading to differences in dissolution rate, chemical reaction rate and mechanical properties. Amorphous solids also have a higher solubility than their crystal form. The solubility advantage compared with the most stable crystalline counterpart was predicted to be from 10 to 1600 fold, as shown by Hancock and Parks (25). However, the experimental solubility advantage was usually considerably less than this, because determining solubility for amorphous materials under true equilibrium conditions is difficult because of the tendency for such materials to crystallize upon exposure to small quantities of solvents.

When particles are in the submicron range, a small increase in the saturation solubility is expected as described by the Freundlich Ostwald equation [eq. (12)] (27,28).

$$\frac{RT}{V_m} \ln \frac{S}{S_0} = \frac{2\gamma}{r} \tag{12}$$

where  $S$  is the saturation solubility of nanosized particle,  $S_0$  is saturation solubility of an infinitely large crystal,  $\gamma$  is the crystal-medium interfacial tension,  $r$  is the particle radius,  $V_m$  is the molar volume,  $R$  is a gas constant, and  $T$  is the temperature. Assuming a molecular weight of 500, density of 1 gm/mL, and a value of 60 to 70 mN/m for the crystal-water interfacial tension, the above equation would predict a 62% to 76% increase in solubility at a particle size of 100 nm.

**IONIZATION AND THE SOLUBILITY PROFILE**

The total solubility of a compound at a particular pH is the sum of the “intrinsic solubility” of the neutral species in solution plus the solubility of the charged species. For a weak base, when the aqueous medium at a given pH is saturated with free base, the total solubility at that pH may be expressed as described [eq. (13)]. The typical solubility profile of a weak base when  $pH > pH_{max}$  is shown in (Fig. 3).

$$S_{base}(pH > pH_{max}) = [B]_s + [BH^+] = [B]_s \left( 1 + \frac{[H_3O^+]}{K_a} \right) \tag{13}$$

When there are counterions present in the solution, at low enough pH, the entire free base will be converted into salt form, and the salt is the solid form. In this case, the equilibrium solubility at a particular pH may be expressed by equation (14).

$$S_{base}(pH < pH_{max}) = [B] + [BH^+]_s = [BH^+]_s \left( 1 + \frac{K_a}{[H_3O^+]} \right) \tag{14}$$

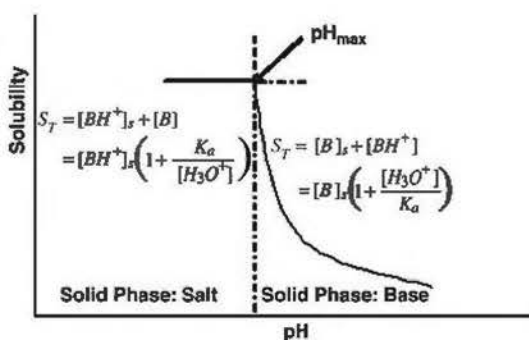


Figure 3 Schematic representation of the pH solubility profile of a weakly basic compound.

Downloaded from informahealthcare.com by McGill University on 01/15/13  
For personal use only



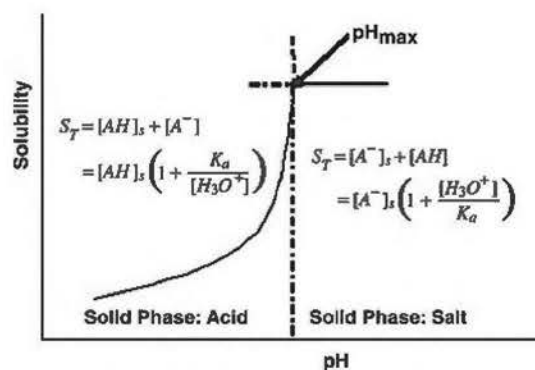


Figure 4 Schematic representation of the pH solubility profile of a weakly acidic compound.

When these two independent curves in solubility pH profile intersect, the point is called  $\text{pH}_{\text{max}}$  as shown in the Figure 3. Similarly, the pH-solubility profile for a weak acid is also shown (Fig. 4).

Zwitterions refer to compounds with oppositely charged groups, but carry a total net charge of 0 and is thus electrically neutral. Solubility of zwitterions at certain pH is the combination of the contributions from all the charge groups. For compounds with two ionizable groups, solubility can be expressed by the following equation [eq. (15)].

$$S = S_0(1 + 10^{\text{p}K_{a1} - \text{pH}} + 10^{\text{pH} - \text{p}K_{a2}}) \quad (15)$$

It depends on its ionization constants, pH and intrinsic solubility,  $S_0$ , which is defined as the solubility of the neutral form of the compound. The solubility profile is U-shape characteristic for zwitterionic compounds.

For weak electrolyte drugs, salt formation is a common approach to improve solubility. Acids form salts with basic drugs and bases form salts with acidic drugs (29). For the salt of a basic drug, the dissolution equilibrium can be described as equation (16).



Where  $[\text{BH}^+]_s$  is the salt solubility and  $[\text{X}^-]$  is the counterion concentration. The apparent solubility product  $K_{\text{sp}}$  can be derived as equation (17).

$$K_{\text{sp}} = [\text{BH}^+]_s [\text{X}^-] \quad (17)$$

In the absence of excess counterion,  $[\text{BH}^+]_s = [\text{X}^-]$ , solubility is the square root of  $K_{\text{sp}}$ . Under such conditions, drug solubility does not change with pH, as indicated in the figures above. On the other hand, if a significant amount of counterions exist in the formulation, decrease in solubility may be observed according to equation (18).

$$[\text{BH}^+]_s = K_{\text{sp}} / [\text{X}^-] \quad (18)$$

### SOLUBILITY PREDICTION

A number of approaches to solubility prediction have been developed over the years and continue to be used (30). Recently many successful attempts were made for predicting aqueous solubility of compounds, but it is still a challenge to identify a single method that is best at predicting aqueous solubility (31). The first hurdle in the prediction of aqueous solubility is the estimation of melting point or enthalpy of sublimation (32). In addition, it is difficult to predict the solubility of a complex drug candidate on the basis of the presence or absence of certain functional groups. Conformational effects in solution may play a role in solubility and cannot be accounted for by a simple summation of contributing groups.

Because of the complexity involved in developing the prediction models, most models were completed using nonelectrolytes.

The prediction of aqueous solubility tends to use three approaches: methods correlating experimentally determined melting points and  $\log P$ , correlations based on group contributions, and correlations with physicochemical and quantum chemical descriptors calculated from the molecular structure [quantitative structure property relationship (QSPR) approaches] (1).

Methods using melting point and  $\log P$  are best exemplified by the general solubility equation (GSE) model (33). The GSE model is based on the fact that the aqueous solubility of a nonelectrolyte solute depends on its crystallinity and its polarity, wherein the melting point and the octanol-water partition coefficient act as good surrogate measures, respectfully. For compounds with melting points  $< 25^\circ\text{C}$ , the melting point is taken to be  $25^\circ\text{C}$ . Ran, Yalkowsky and coworkers (34) revised equation 11 to equation (19).

$$\text{Log}S = 0.5 \log P_{ow} - 0.01(\text{MP} - 25) \quad (19)$$

The theoretical treatment of this solubility prediction method is presented in more details elsewhere (1). With this prediction model, the absolute average error ranged from 0.5 to 1 log molar solubility unit for drug-like compounds (35).

The aqueous functional group activity coefficients (AQUAFAC) model is based on group contribution values, which are based on experimental aqueous solubilities (36). In this model, the molar aqueous solubility can be calculated using equation (20).

$$\text{Log}S = 1.74 \log \gamma_w + \frac{\Delta S_m(T_m - T)}{2.303RT} \quad (20)$$

Where,  $\gamma_w$  is the aqueous activity coefficient of a compound, which is obtained from the AQUAFAC model.  $\Delta S_m$  is the entropy of melting,  $T_m$  is the melting point, and  $T$  is the ambient temperature, both in Kelvin,  $R$  is the gas constant.

Using QSPR models, aqueous solubility is controlled predominantly by solute molecular size and shape, by its polar nature and hydrogen bonding capabilities. In addition, hydrophobicity, flexibility, electron distribution and charge have been found to play important roles in prediction (37). Many molecular property descriptors are now available computationally. Aqueous solubility has been modeled by correlating measured solubilities with one or more physicochemical and/or structure properties. Most methods use linear methods such as multiple linear regression (PLS) or nonlinear methods such as artificial neural networks (ANN). In general, nonlinear methods appear to provide better predictions (38). The root mean squared errors for models based on QSPR tends to range from approximately 0.7 log units to 1 log units. Recently, the effect of crystal packing on solubility has been added into the computational model (39).

Jain et al. applied two methods to compare aqueous solubility estimation of 1642 organic nonelectrolyte compounds ranging from  $10^{-13}$  to  $10^0$  in experimental molar solubility (33). The average absolute errors in the solubility prediction are 0.543 log units for AQUAFAC and 0.576 log units for the GSE. About 88.0% of the AQUAFAC solubilities and 83.0% of the GSE molar solubilities are predicted within one log unit of the observed values. The marginally better accuracy of AQUAFAC is assumed to be due to the fact that it utilizes fitted-parameters for many structural fragments and is based on experimental solubility data. The AQUAFAC also includes reasonable estimate of the role of crystallinity in determining solubility. The GSE on the other hand is a simpler, nonregression based equation, which uses two parameters (MP and  $\log K_{ow}$ ) for solubility prediction. The major assumption in the GSE is that octanol is an ideal solvent for all the solutes. This may not be true for strongly hydrogen bonding compounds, and consequently might result in larger error for such compounds.

With some computational packages it is now possible to make predictions on aqueous solubility that are as good as experimental measurements ( $\pm 0.5$  log unit) for many compounds. However, all of the commercial programs were trained on selected organic chemicals and the predictive ability for drug-like compounds is still a challenge. When the commercial software programs do not yield good results for internal compounds, it may be necessary to evaluate various QSAR models and develop an in-house model (30).

## SOLUBILIZATION AND "ENHANCED SOLUBILITY"

### Modifications to the Solid State

Salt formation is probably the most common way to increase both the solubility and dissolution rate of ionizable drugs (29). The solid form, clearly distinct from the free acid or base solid form, provides significant enhancement in solubility through the provision of alternative equilibria, thus driving the total solubility (intrinsic + ionized) up significantly. This alternative equilibria results in a more readily solvated ionized form in hydrolytic solvents. As discussed earlier, the saturation solubility of the salt will be defined in conjunction with the  $K_{sp}$ , resulting pH and relative  $pK_a$  of the drug. As shown earlier (Figs. 3 and 4), changes in the pH or media composition can alter the solubility through common ion effects, or if the pH deviates well away from the  $pK_a$ , can actually result in precipitation of the free acid or base solid.

Selection of the counterion can actually be used to control the solubility by varying the  $K_{sp}$ . As pointed out by Anderson and Conradi (40), the impact of hydrogen bonding within the conjugate species can play a role in the  $K_{sp}$  and ends up also being translated into effects on the melting point of the salt. Common ion effects are manifested through the relationship defined by the  $K_{sp}$ . The solubility of the hydrochloride salt of the zwitterionic molecule lomefloxacin is a good example where excess chloride ion, as in admixtures with normal saline, can impact the solubility of the salt (41) (Fig. 5).

It is important to recognize that with any salt, the resulting pH of the media will be paramount in avoiding precipitation of the free base or acid. The strong acid conjugate salt of a weakly basic drug will end up driving the pH of the solution acidic, and conversely for strong base conjugate of weakly acidic drug. Care must be taken when such salts are dissolved into buffered systems where supersaturated solutions of the free base or acid may occur and have the propensity to precipitate with time. In such cases, a full understanding of the solubility versus pH curve is critical when using salts to provide improved solubility.

Cocrystals, similar to salts, provide a means to generate a crystalline form of the drug. While these solid phases can provide increased dissolution rates there has been minimal use of cocrystals to facilitate parenteral drug delivery. The properties and description of cocrystals has been discussed at length in a recent review (42).

The use of high energy amorphous solids can often result in temporary increases in solubility, but with a propensity to generate more stable crystalline forms. In parenteral

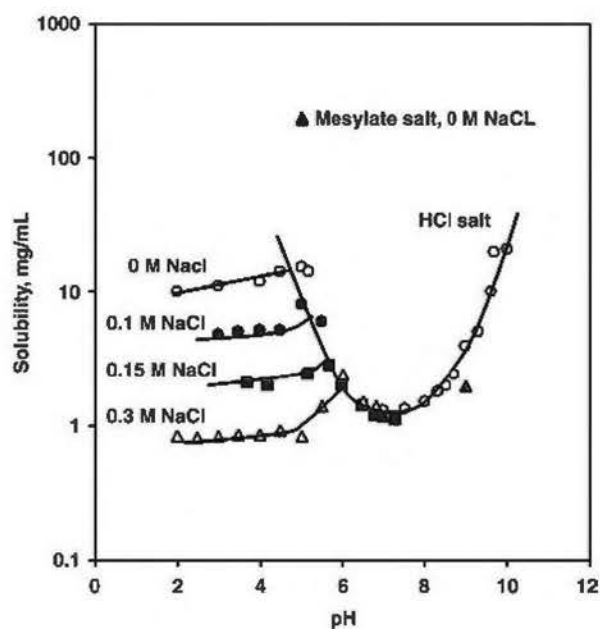


Figure 5 Effect of pH and NaCl concentration on the solubility of the zwitterionic quinolone lomefloxacin. Source: From Ref. 41.

products, the importance of metastable solids can many times play a role with lyophilized products upon reconstitution. The process of lyophilization often results in higher energy polymorphs or amorphous solids which allow for a very rapid dissolution and reconstitution back to the solution state. A thorough understanding of the dynamic nature of the lyophilized solid forms and the more stable crystalline forms which may exist is critical, whether they are hydrates, solvates, or polymorphs. The intentional use of such high energy states to increase solubility is limited because of its unpredictable behavior.

The best way to adjust solid form and impact solubility is via molecular modification, either as an analog or through formation of a prodrug. While these must be considered new chemical entities, they can provide a broad range of possible properties. Analog strategies are often focused on attempts to either decrease the lipophilicity and/or introduce hydrogen bonding groups which can enhance solvation in more hydrophilic media. In either case, especially with introduction of hydrogen bonding groups, increased interactions in the solid phase and its melt can actually increase as well, thus offsetting any gains afforded by increases in solvation. When possible, the introduction of ionizable groups can provide great solubility advantages (43).

In those cases where the perservation of the pharmacophore or desired biopharmaceutical properties does not permit molecular modifications leading to a more soluble molecule, a prodrug strategy can be invoked, overcoming immediate solubility limitations, yet when appropriately triggered, can release the active parent of interest (44).

#### Modifications to the Solution Phase

The use of cosolvents as was discussed earlier, has the ability to alter the dielectric constant of the solvent, influence the energy required to overcome hydrogen bonding forces in aqueous media and reduce the amount of energy necessary to create a cavity sufficient to accommodate the solute. Furthermore, these changes in solvent can greatly alter the degree of solvation of the solute once molecularly dispersed in the solvent. Solubility enhancement by addition of cosolvent is very typically log linear with respect to the cosolvent (Fig. 6). The degree of solubilization is dependent on both the lipophilicity, or  $\log P$ , of the drug and type of cosolvent (45) (Fig. 6). Cosolvency and solubilization have been discussed by Rubino (46).

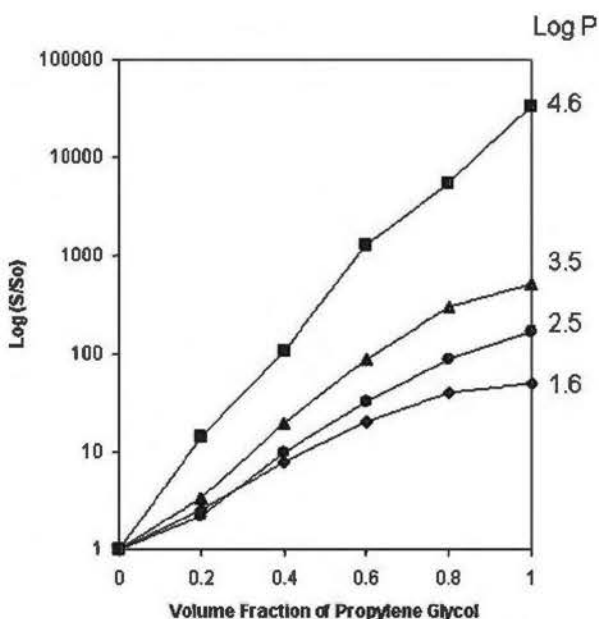


Figure 6 Propylene glycol solubilization of hydrocortisone esters. Source: From Ref. 45.

### Modification due to Alternative Equilibria for Solute

An excellent overview of various methods to provide alternative equilibria for solubilization was presented by Yalkowsky (1). The rational selection of a solubilizing agent should be based on the structure of the drug to be solubilized and on the degree of solubilization needed to obtain the desired dose. The generation of alternative equilibria for the drug to exist in is one of the most commonly used methods to provide enhancements in the overall “apparent solubility” of the drug in solution. This strategy includes the use of ionization equilibria (discussed above in conjunction with salts), complexation equilibria, partitioning into surfactant micelles, partitioning into emulsion systems, and liposomal type systems.

#### Complexation and Association

Strategies of complexation include the use of chelating agents, organic molecular associations and inclusion complexes. The most common formulation strategies using complexation are centered around the use of cyclodextrins, with more emphasis generally placed on derivatized cyclodextrins because of their greater solubility and improved in vivo safety margin. Typically only those drugs with an aromatic ring or a nonpolar side chain are solubilized by cyclodextrin complexation (4). If complexation alone is insufficient, then a combination of complexation and pH modification or/and cosolvent may be used (47).

Complexation is an equilibrium process and the binding constant (or stability constant) for the formation of a 1:1 complex is given by equation (21).

$$\kappa_{1:1} = \frac{[\text{Drug}]_{\text{complex}}}{[\text{Drug}]_{\text{free}}[\text{Ligand}]_{\text{free}}} \quad (21)$$

$[\text{Drug}]_{\text{free}}$ ,  $[\text{Ligand}]_{\text{free}}$  and  $[\text{Drug}]_{\text{complex}}$  ( $m$  molecules of drug,  $n$  molecules of ligand) are the equilibrium molar concentrations of the free drug, the ligand and the drug in the complex form, respectively. Often, it is impossible to separate the individual binding constants and the apparent binding constant ( $\kappa_{\text{app}}$ ) is used [eq. (22)].

$$\kappa_{\text{app},m:n} = \frac{[\text{Drug}]_m [\text{Ligand}]_n]_{\text{complex}}}{[\text{Drug}]^m [\text{Ligand}]^n} \quad (22)$$

The total solubility of the drug in the presence of ligand is the sum of the intrinsic solubility of the drug in the absence of the ligand and the solubility of the drug in the ligand(s) [eqs. (23) and (24)].

$$[\text{Drug}]_{\text{total}} = [\text{Drug}]_{\text{intrinsic}} + \tau [\text{Ligand}]_{\text{total}} \quad (23)$$

$$\tau = \frac{m\kappa_{\text{app},m:n} [\text{Drug}]_{\text{intrinsic}}^m}{1 + \kappa_{\text{app},m:n} [\text{Drug}]_{\text{intrinsic}}^m} \quad (24)$$

A plot of  $[\text{Drug}]_{\text{total}}$  versus  $[\text{Ligand}]_{\text{total}}$  gives an intercept of  $[\text{Drug}]_{\text{intrinsic}}$  and a slope  $\tau$ . According to the above equation, the total solubility of a drug undergoing complexation is a linear function of the ligand concentration. The intercept of this line is equal to the solubility of the free drug and its slope is given by  $\tau$ . Rearrangement of the equation allowed the calculation of the apparent binding constant,  $\kappa_{\text{app},m:n}$  [eq. (25)].

$$\kappa_{\text{app},m:n} = \frac{\tau}{m[\text{Drug}]_{\text{intrinsic}}^m \tau [\text{Drug}]_{\text{intrinsic}}^m} \quad (25)$$

The value of  $\kappa$  is a measure of the strength of the drug-ligand interactions and is dependent on the properties of the drug and the ligand molecules. For a particular ligand, the size, shape, aromaticity and the nonpolarity of the drug molecule play important roles in determining this strength. The properties of the solubilizing medium, such as temperature and polarity also influence the strength of these interactions (48–50).

Complexation of lomefloxacin with five metal ions ( $\text{Al}^{3+}$ ,  $\text{Ca}^{2+}$ ,  $\text{Mg}^{2+}$ ,  $\text{Bi}^{3+}$ , and  $\text{Fe}^{3+}$ ) was found to increase solubility of lomefloxacin (50). The stoichiometrics of the various complexes were different. In the presence of 0.25 M  $\text{Ca}^{2+}$  ion, solubility of lomefloxacin was raised by two to threefold at pH 5, while 0.25 M  $\text{Al}^{3+}$  increased the solubility by nearly 30 fold. The stability constants were determined from the solubility, which ranged from 11.2 for L: $\text{Ca}^{2+}$  complexes to  $2.34 \times 10^{10}$  for L: $\text{Al}^{3+}$  complexes. The authors concluded that the higher order of stability for lomefloxacin-Al ion complex was related to the higher charge density of the metal ion.

Hydrotropic agents (hydrotropes) have been used to increase the water solubility of poorly soluble drugs, and in many cases, the water solubility has increased by orders of magnitude (51). Several hydrotropic agents such as urea, caffeine and other xanthine derivatives, tryptophan, sodium benzoate, PABA-HCl, Procaine-HCl and nicotinamides have been identified. Solubilization diagram for riboflavine exhibits a positive deviation from linearity, which implies a greater solubilizing power at higher concentrations of PABA-HCl and is characteristic of hydrotropic solubilization (52). In the study to increase the solubility of paclitaxel, 5.95 M of *N,N*-doethylnicotinamide was found to raise the solubility by 1700 fold (from 0.30  $\mu\text{g}/\text{mL}$  to 512  $\text{mg}/\text{mL}$  or 0.6 M). The authors indicated that an effective hydrotropic agent should be highly water soluble while maintaining a hydrophobic segment (51). Almost all highly effective hydrotropic agents have a pyridine or a benzene ring in their structure.

Complexation of a drug molecule with a ligand molecule reduces the exposure of former's hydrophobic region to water resulting in an increase in its solubility. The practical and phenomenological implications of phase-solubility analysis were developed by Higuchi and Connors in their pioneering work published in 1965 (53). On the basis of the shape of the generated phase-solubility relationships, several types of behaviors can be identified (Fig. 7). The two major types are A and B. Only A-type of profile will be discussed in this Chapter.

In an A-type system, the apparent solubility of the substrate increases as a function of CD concentration. In  $A_L$  subtype, the solubility is increased linearly as a function of solubilizing concentration.  $A_P$  system indicates an isotherm wherein the curve deviates in a positive direction from linearity and the  $A_N$  system indicates a negative deviation from linearity. The equations related to complexation with cyclodextrin were presented in the previous section except that the ligand is replaced with cyclodextrin.

The use of CDs to enhance solubilization of a poorly soluble drug is often preferred to organic solvents (54). As a solution is administered, both the drug and CD concentration are reduced in a linear manner making precipitation is less likely. Drug release from parenteral administration of CD complexes is thought to be associated with complete and almost instantaneous dissociation via the dilution of the complex (49). For strongly bound drugs, or for those cases where dilution is minimal, contributions from competitive displacement by endogenous materials, drug binding to plasma and tissue components, uptake of the drug by tissue not available to the complex or CD, and CD elimination may also be important (55). In ophthalmic applications where the possibility for dilution is more limited, factors associated with partitioning and secondary equilibria may be the main mechanisms for drug release.

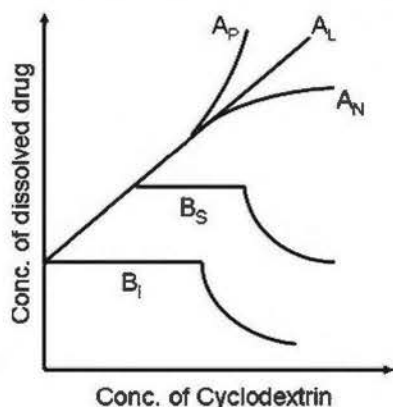


Figure 7 Graphical representation of A and B type phase solubility profiles with applicable subtypes ( $A_P$ ,  $A_L$ ,  $A_N$ , and  $B_S$ ,  $B_I$ ). Source: From Ref. 53.

Inclusion complexation is restricted to drugs that have a hydrophobic region that can be inserted into a cavity that has the fixed dimensions. For  $\alpha$ -,  $\beta$ -, and  $\gamma$ -cyclodextrins, the cross section of the solute protrusion must be less than 6, 8, and 10 Å, respectively. The  $\alpha$ CD can preferentially accommodate aliphatic chains, and the  $\beta$ CD accommodates aromatic rings most efficiently. Fused ring or branched compounds can often best accommodate in the larger  $\gamma$ CD cavity. Modified cyclodextrins are very water soluble and form moderately nonviscous solutions (1). Because of the large molecular weight and relatively high cost of cyclodextrins, their use is generally limited to solutes for which a low molar solubility is desired.

Cyclodextrins are cyclic oligosaccharides derived from starch containing six ( $\alpha$ CD), seven ( $\beta$ CD), eight ( $\gamma$ CD), nine ( $\delta$ CD), ten ( $\epsilon$ CD) or more ( $\alpha$ -1,4)-linked  $\alpha$ -D-glucopyranose units (54). In addition to increase the aqueous solubility of poorly water-soluble drugs and stability, CDs can be used to reduce or prevent irritation and prevent drug-drug interactions (56). The central cavity of the CD molecule carries lipophilic characteristic (57). In aqueous solution, the hydroxy groups form hydrogen bonds with the surrounding water molecules resulting in a hydration shell around the dissolved CD molecule (54). In general, the natural cyclodextrins exhibited less than 10-fold improvement in the solubility of compound.

The rates of formation and dissociation of drug:CD complexes are very close to diffusion rate-controlled with drug: CD complexes continuously being formed and broken apart (55). The equilibrium constants were reported to have a mean value of 130, 490 and 350 M<sup>-1</sup> for  $\alpha$ CD,  $\beta$ CD and  $\gamma$ CD (58). A marketed parenteral solution, Caverject Dual<sup>®</sup> (alprostadil IV solution), contains  $\alpha$ CD in which  $\alpha$ CD is mainly excreted unchanged in the urine after IV injection and it has a higher solubility of 145 mg/mL at 25°C in water (59).  $\beta$ CD is limited in its parenteral application by its low aqueous solubility of 18.5 mg/mL at 25°C and adverse nephrotoxicity.

The natural CDs and their complexes are of limited aqueous solubility. Substitution of the hydrogen bond-forming hydroxyl groups results in improvement in their aqueous solubility. Modified CD include the hydroxypropyl derivatives of  $\beta$ CD (HP $\beta$ CD) and  $\gamma$ CD (HP $\gamma$ CD), the randomly methylated  $\beta$ CD (RM $\beta$ CD) and sulfobutylether  $\beta$ CD (SBE $\beta$ CD) (54). The modified cyclodextrin has been reported to increase solubility of progesterone by 3600 fold in with 300 mM of HP $\beta$ CD (60). HP $\beta$ CD and SBE $\beta$ CD are considered nontoxic at low to moderate i.v. doses (54). HP $\beta$ CD and SBE $\beta$ CD are much more water soluble than natural  $\beta$ CD and have been used in several parenteral products, including Itraconazole (Sporanox) and Voriconazole (Vfend<sup>®</sup>, containing 16%w/v SBE $\beta$ CD). After i.v. injection, HP $\beta$ CD is almost exclusively eliminated through the kidneys. HP $\gamma$ CD has been incorporated in an eye drop solution and a parenteral diagnostic product.

Cyclodextrins can be used in combination with pH adjustment for synergistic drug solubility enhancement, according to the following equation [eq. (26)].

$$[\text{Drug}]_{\text{total}} = [\text{Drug}_u] + [\text{Drug}_i] + [\text{Drug}_u\text{CD}] + [\text{Drug}_i\text{CD}] \quad (26)$$

Where [Drug<sub>u</sub>CD] is unionized drug-cyclodextrin complex, and [Drug<sub>i</sub>CD] is ionized drug-cyclodextrin complex. The synergistic effect is generated because of the ionized drug-ligand complex [Drug<sub>i</sub>CD], which is absent in situations where pH adjustment or cyclodextrin is used alone (61). The interactions of charged and uncharged drugs with neutral (HP $\beta$ CD) and anionically charged (SBE $\beta$ CD) modified  $\beta$ -cyclodextrins have been studied (62). The authors found the binding constants for the neutral forms of the drugs to be greater with SBE $\beta$ CD than with HP $\beta$ CD. For the anionic drugs, the binding constants between SBE $\beta$ CD and HP $\beta$ CD were similar, while the binding constants for the cationic agents with SBE $\beta$ CD were superior to those of HP $\beta$ CD. Therefore, a clear charge effect on complexation, attraction in the case of cationic drugs and perhaps inhibition in the case of anionic drugs, was seen with the SBE $\beta$ CD.

#### Micellar

If a drug is not solubilized by aqueous pH-modification, cosolvents, complexation, or combinations of these, surfactants are often used. The formulations are usually concentrated drug solutions in water-miscible organic solvent(s) that are diluted prior to intravenous administration (4). Water-miscible surfactant molecules contain both hydrophilic and

hydrophobic portions which self-associate to form micelles once the surfactant monomer concentration reaches the critical micelle concentration (CMC). Surfactants in parenterals can increase drug solubility through micellization, improve drug wetting, prevent drug precipitation upon injection, improve the stability of a drug in solution, modulate drug release or to prevent aggregation due to liquid/air or liquid/solid interfacial interactions (63).

A simple equation illustrates the principle of surfactant induced micellization and its impact on drug dissolution is as follows [eq. (27)].

$$[\text{Drug}]_{\text{total}} = [\text{Drug}]_{\text{aqueous}}(1 + \kappa[\text{Surfactant}]_{\text{m}}) \quad (27)$$

Where  $[\text{Drug}]_{\text{total}}$  is the total solubility,  $[\text{Drug}]_{\text{aqueous}}$  is the drug aqueous solubility,  $\kappa$  is a distribution coefficient,  $[\text{Surfactant}]_{\text{m}}$  is the difference between the surfactant concentration and the CMC. The total drug in solution increases linearly with the linear increase in surfactant concentration once the surfactant concentration exceeds the CMC. While the linear response limits the degree of solubilization, it minimizes the potential for supersaturation or precipitation upon dilution.

The surfactants commonly used for intravenous infusion formulation include cremophor EL, cremophor RH60, and polysorbate 80. The solubilizing solvent is typically a mixture of surfactant and solvent(s) such as cremophor EL/ethanol/propylene glycol. The upper limit of surfactant administered in vivo is 10% for the cremophor EL and up to 25% polysorbate 80 for IV infusion. Cremophor EL is known to have significant side effects such as hypersensitivity reactions and liver damage (64).

Polysorbate 80 is a nonionic surfactant commonly used in parenteral formulations. Chlordiazepoxide (Librium<sup>TM</sup>) comprises 4% of polysorbate 80 along with 20% propylene glycol and is injected undiluted intramuscularly. Quite often the surfactant containing formulation is diluted prior to intravenous administration to reduce toxicity. For example, amidarone hydrochloride has a water solubility of 0.7 mg/mL, is solubilized to 50 mg/mL in Cordarone<sup>TM</sup> by a combination of 10% polysorbate 80 and pH adjustment to 4.1. It is administered by intravenous infusion after a 25-fold dilution with dextrose 5%. Solutol HS-15 is a newer nonionic surfactant for parenteral formulation. Solutol HS-15 is used up to 50% to solubilize Propanidid, 7% to solubilize Vitamin K<sub>1</sub>. Solutol HS-15 has also been used in preclinical formulations to prepare supersaturated injectable formulations of water-insoluble molecules (65).

#### Emulsions

Highly lipophilic, low melting point drugs can be quite soluble in oils and formulated for intravenous administration by employing an oil-in-water emulsion stabilized by surfactants in interfacial phases. A recent review by Strickley provides an excellent summary of excipients used in commercially available lipid-based formulations (4). Emulsions typically contain 10% to 20% oil and 2% glycerol for isotonicity, 1% phospholipid surfactant (e.g., lecithin), at pH 7 to 8 and an oil-soluble drug partitioned into the oil phase. The surfactant is applied to provide an energy barrier to agglomeration of the emulsion droplets. Lipid-based systems can exist in a wide variety of microstructures depending on the components used and their concentration, such as w/o or o/w emulsion and microemulsions, micelles, reverse micelles, bicontinuous phases, or mesomorphic phases (66). The solubilization capacity and drug release rate of the active molecules are related to the microstructure. Understanding solubility in lipid mixture is complicated by the fact that these systems are strongly affected by their interfacial nature, the nature of the oil, surfactant, cosurfactant, the size of the droplet and the preferred location of the drug within the system (67). The unique structural organization of the microemulsion results in additional domains which may increase their solubilization capacity as compared with nonstructured solutions containing the same fraction of components.

A marketed emulsion in the United States, Diprivan<sup>®</sup>, in which propofol, a water-insoluble compound is solubilized to 10 mg/mL in an emulsion composed of 10% soybean oil, is administered by IV bolus or IN infusion (4). There are other commercial emulsions in Europe and Japan, including diazepam, PGE1, dexamethasone palmitate and flurbiprofen.

Emulsions are being prepared with an energy input, such as ultrasonication, homogenization, or high-speed stirring and are thermodynamically unstable because of high



interfacial energy. Stabilization hinges on the ability to reduce interfacial tension, forming an interfacial film barrier to kinetically impede coalescence of droplets. There are four types of stabilizing agents: inorganic electrolytes, surfactants, macromolecules and solid particles. Detailed discussion is available elsewhere (68).

Microemulsions are a thermodynamically stable isotropically clear dispersion composed of a polar solvent, an oil, a surfactant, and a cosurfactant. The potential to form self-emulsifying drug delivery systems was evaluated by Pouton in 1985 (69). Recently, development of injectable microemulsions has received considerable attention for IV delivery of drugs because of its potential to increase solubility (e.g., solubility of felodipine was increased by 10,000 fold in the microemulsion), reduce toxicity and hypersensitivity, reduce pain upon injection, as a long circulating formulation for drug targeting, and as a depot for IM delivery of drugs (70-72).

Microemulsions offer many advantages compared with macroemulsions: smaller particles (often <100 nm), require less energy to process and have higher physical stability (73). Microemulsions generally have very low interfacial tension at the water-oil interface, and form a highly fluid interfacial surfactant film. Because of the numerous small droplets, the surface area to volume ratio of microemulsions are very high and it forms easily because of the low surface tension, typically due to high levels of surface active species.

Most drugs that can be formulated in emulsions are generally liquids or low melting solids that have high octanol-water partition coefficients (74). In the Diprivan emulsion, Propofol has a high solubility in vegetable oil (>0 mg/mL), a low melting point of 18°C, and a large octanol-water partition coefficient ( $\log P$  3.83 in pH 6-8.5). Drugs with moderate to high melting point often cannot be formulated as emulsions because of the high lattice energy and low solubility in oil. High melting drugs possess some degree of polarity (i.e., presence of permanent dipoles and ability to form hydrogen bond), and these strong intermolecular forces cannot be readily overcome by the weak dispersion forces operating between solute and oil. Malcolmson studied the effect of oil on the solubility of testosterone propionate in nonionic o/w microemulsions and reported that larger molecular volume oils such as triglycerides miglyol 812 significantly increased the solubility of the compound over the corresponding micellar solution (75).

Predicting the solubility in lipid emulsions may be quite complicated because of the interfacial nature of the systems and the distribution of the drug in the continuous or dispersed phase and sometimes preferred location at the surfactant interface (67). If the drug preferentially resides at the interface in microemulsions, the creation of a larger interfacial area upon mixing the components may result in higher solubility. Testard studied the solubilization of a lipophilic molecule, lindane, in a microemulsion with a nonionic surfactant. They found the solubility of lindane increased in the microemulsion region compared with the bulk oil; it was attributed to the incorporation of lindane in the surfactant interface (76). Addition of an amphiphilic block copolymer to medium chain surfactants has been shown to favorably alter the interfacial structure and significantly boost the solubilization capacity of microemulsions (77).

Surfactants are added to emulsion systems to reduce interfacial tension, reduce initial droplet size and size distribution, draw a liquid film between droplets in areas where film thinning may have occurred, impart steric stabilization and in the case of charged surfactants give rise to charge distribution. The presence of surfactant and cosurfactant could make microemulsion supersolvents for drugs relatively insoluble in both aqueous and hydrophobic solvents (78). Using mixed oils and/or mixed surfactants in microemulsion may offer significant advantages over using pure single component materials (79). Prediction of absolute solubility in lipid vehicles is difficult since it requires similar knowledge as needed for aqueous solubility prediction, but also knowledge of the drug's specific interactions between the solute and formulation components, including an understanding of the lipid microstructure (67).

#### *Liposome*

Liposome formulations can be used as a means to solubilize some drugs for intravenous administration, to improve pharmacokinetics, enhance efficacy, and reduce toxicity (4). Liposomes are closed spherical vesicles composed of one or more bilayers of amphipathic lipid molecules enclosing one or more aqueous core compartments (80). 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 as an integral part of the lipid bilayer. Water-soluble drugs reside within the aqueous inner core and are released as the liposome erodes in vivo or by leakage. A typical liposome formulation contains water with phospholipid at ~5 to 20 mg/mL, an isotonicifier, a pH 5 to 8 buffer, and potentially cholesterol.

Liposomes are injected either by IV infusion or intrathecally. Upon IV administration, most conventional liposomes are easily taken up by the reticuloendothelial system (RES, in the body). There are several liposome formulations on the market. Amphotericin B, a compound with low aqueous solubility of ~0.1 mg/mL at pH 2 (anion) or pH 11 (cation), is solubilized to 5 mg/mL by liposomal intercalation and becomes an integral part of the lipid bilayer (81). The amphotericin B liposomal products are being administered by IV infusion and have a longer in vivo half-life. Upon formulation in liposomes, paclitaxel, a low solubility drug (< 2 µg/mL), has been reported to achieve a solubility of 3.39 mg/mL in a liposomal formulation of polyethylene glycol 400, soybean phosphatidylcholine (PC) and cholesterol (82). Liposomes can be classified on the basis of liposome size or lamellarity as multilamellar large vesicles (MLVs), small unilamellar vesicles (SUVs), and large unilamellar vesicles (LUVs).

The lipids normally used are the unsaturated PC, phosphatidic acid (PA), phosphatidylglycerol (PG), and the saturated lipids L-α-dimyristoylphosphatidylcholine (DMPC), dipalmitoyl phosphatidylcholine (DPPC), dipalmitoyl phosphatidic acid (DPPA), and L-α-dimyristoylphosphatidylglycerol (DMPG). ABELCET<sup>®</sup> is an example of MLV consists of amphotericin B complexed with DMPC and DMPG in a 1/0.7/0.3 molar ratio. The complex assumes a flattened, ribbon-like multilamellar structure with a particle size ranging from 1600 to 11,000 nm. Upon administration, ABELCET exhibits large volume of distribution, high clearance from blood and long terminal elimination half-life.

Large unilamellar liposomes (LUV) refer to vesicles > 100 nm in diameter bounded to single bilayer membrane. LUV provides higher encapsulation of water-soluble drugs, economy of lipids and reproducible drug release rates; however, these LUV liposomes are difficult to produce. Small unilamellar liposomes (SUV) are formed by dispersing multilamellar vesicles into water using sonication, extrusion through filters of various pore sizes, or homogenization to form optically clear suspensions. AmBisome<sup>®</sup> is an example of closed fluid-filled unilamellar bilayer liposomes made of a single phospholipid bilayer with amphotericin B intercalated within the membrane at drug:lipid molecular ratio 1:9, and particle size 45 to 80 nm. Upon injection, AmBisome exhibits smaller volume of distribution than the multilamellar ABELCET. Several excellent reviews on liposome technology and its application have been published (83,84).

#### Combined Solubilization Strategies

Various methods have been reported to enhance solubility of poorly soluble compounds by utilizing a combination of more than one of the solubilization techniques (54,85,86).

Combined use of pH with surfactants was reported to significantly increase drug solubility. The total solubility of a weak electrolyte undergoing ionization and micellization can be accounting for the free unionized drug  $D_u$ , free ionized drug  $D_i$ , micellized unionized drug  $D_uM$ , and micellized ionized drug  $D_iM$  as equation (28).

$$[\text{Drug}]_{\text{total}} = [\text{Drug}_u] + [\text{Drug}_i] + K_u[\text{Drug}_u][M] + K_i[\text{Drug}_i][M] \quad (28)$$

where  $K_u$  and  $K_i$  are the micellar equilibrium constants for the unionized and ionized drug, respectively. This equation is valid for surfactants that are either neutral or completely ionized in the pH range studied. Li discussed this approach using polysorbate 20 on flavopiridol, a weakly basic compound with an apparent  $pK_a$  of 5.69 and a low intrinsic solubility of 0.025 mg/mL for its zwitterionic form (87). The solubility of flavopiridol in 10% polysorbate 20 solution at pH 4.3 (27.3 mM) is much higher than that could be expected by increasing the total solubility through appropriate pH adjustment from pH 8.4 and solubilization of the unionized drug in the micelles (3.3 mM). The authors pointed out that high solubility of the ionized drug in the micelles is the source of synergism for solubility enhancement in the

pH-surfactant solutions. Furthermore, this formulation does not precipitate upon dilution with isotonic Sorensen's phosphate buffer.

Combination usage of pH control and cosolvent has been reported to increase solubility of flavopiridol (87). Since solubility of the unionized form is pH independent, the authors concluded the higher total solubility at low pH is attributed to the solubilization of the ionized species by the cosolvent. The pH related solubilization produced by cosolvent can be described by equation (29).

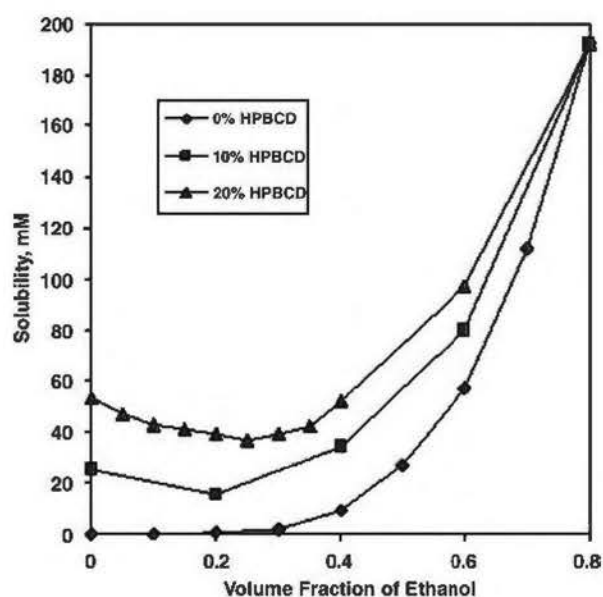
$$[\text{Drug}]_{\text{total}} = [\text{Drug}_u]10^{\sigma_u f} + [\text{Drug}_i]10^{(pK_a - \text{pH})}10^{\sigma_i f} \quad (29)$$

Where  $f$  is the volume fraction of cosolvent,  $\sigma_u$  and  $\sigma_i$  are the solubilizing powers of the cosolvent for the unionized and the ionized species, respectively.

Redenti reported that hydroxylcarboxylic acids (such as citric acid, lactic acid, malic acid, tartaric acid), or bases (such as tromethamine, diethanolamine, triethanolamine) can be used in drug-cyclodextrin solutions to enhance drug solubility by several orders of magnitude through formation of a "multicomponent complex" while that of cyclodextrin can be enhanced more than 10 fold (54). The synergistic effect was rationalized due to the specific interaction of the hydroxyl acid groups with the hydrogen bond system of the host and/or the modification of the hydrogen bond network of the surrounding water molecules. Astemizole, upon  $\beta$ CD multicomponent complexation with tartaric acid, achieved 27,600-fold enhancement of solubility. The resulting amorphous complex dissolved rapidly and generated supersaturation that remains stable for several days.

Loftsson reported that addition of small percentage of hydrophilic polymers in cyclodextrin-based formulation can further enhance drug solubility (88). With the addition of 0.25% polyvinylpyrrolidone, the solubility of a number of compounds was increased from 12% to 129% in a 10% (w/v) HP $\beta$ CD vehicle. The authors suggested that the polymer increased the stability constants of the drug-cyclodextrin complexes because of increased negative enthalpy change together with an increased negative entropy change.

Pitha reported that gradual addition of ethanol decreased and eventually abolished the formation of inclusion complexes of testosterone with HP $\beta$ CD in aqueous solutions (89) (Fig. 8). Initially, at ethanol concentration <30%, the solvent acted as a competing for the cavity of HP $\beta$ CD and reduced the solubility of testosterone; at higher ethanol concentrations



**Figure 8** Effect of ethanol on solubilization of testosterone into aqueous solution containing hydroxyl  $\beta$  cyclodextrin. Source: From Ref. 89.

the solubility of testosterone started to rise, in which the dissolution primarily occurred through nonspecific solvent effects.

The effect of pH variation on complexation and solubilization of naproxen (a weak acid with  $pK_a$  4.2) with natural  $\beta$ CD and various neutral, cationic and anionic  $\beta$ CD derivatives, and hydrophilic polymers has been investigated (86). The authors found the presence of 0.1% PVP increased the solubility of naproxen in the presence of 25 mM HP $\beta$ CD complex by approximately 30%, at pH 1.1 and 6.5. This integrated strategy of pH control and polymer addition to the CD complexing medium allows a smaller quantity of CD be used to solubilize a given amount of drug.

Propylene glycol, PEG, ethanol, cremophor EL, cremophor RH60, and polysorbate 80 are water-miscible solvents and surfactants in commercially available injectable formulations. These solvents and surfactants are used in combination with each other, usually as a concentrate for dilution just prior to IV injection (4). In general, the cosolvent increases the CMC of the surfactant and increases solubility of the drug. Paclitaxel, a water-insoluble compound (aqueous solubility of 0.1  $\mu$ g/mL), is solubilized in Taxol<sup>®</sup> to 6 mg/mL (i.e., 60,000-fold aqueous solubility) with 51% cremophor EL and 49% ethanol, and is diluted 5 to 20 fold with dextrose 5% or lactated Ringer's prior to administration. The final dosing formulation of Taxol is a micellar dispersion (90). The combination of cremophor EL and ethanol has also been used to solubilize teniposide, valrubicin, tacrolimus and cyclosporin.

Trace amount of polymer may decrease the precipitation rate (91), stabilize micelles and other type of aggregates in aqueous solutions and increase the solubility of the compounds by about twofold (92). Water-soluble polymers not only solubilize  $\beta$ CD and its complexes, but they are also able to enhance formation of complexes between drugs and  $\beta$ CD (54). Quarternary complexes of drug, cyclodextrin, polymer and tartaric acid have been reported to further enhance drug solubility (93). However, contrary results have been reported that formation of polymer/cyclodextrin complexes reduced the ability of the cyclodextrin to solubilize drug through complexation (54).

#### SUMMARY

The decisions regarding solubilization strategy often reside in the intrinsic solubility of the drug, solubilization capacity of the particular strategy, dose of drug to be delivered, infusion time, and potential safety concerns with the excipients, all coupled with the therapeutic area and unmet need. Technologies such as cosolvency and pH modification (indirectly salts) are often favored because of their very high capacity for solubilization. They typically result in exponential increases in solubility and can be very valuable for very low intrinsic solubility drugs (i.e., less than 10 mcg/mL), leading to apparent solubilities in excess of 50 mg/mL. However, given the exponential nature of solubilization and linear nature of subsequent dilution on administration, they are much more prone to precipitation upon dilution. Other approaches (micellar, complexation, emulsions, liposomes) often have lower capacity, but tend to solubilize in a more linear proportionality to concentration of solubilizer, thus being much less prone to precipitation upon dilution. These more linear alternative equilibrium type approaches are not likely to provide solubilization in excess of 20 mg/mL, often much less.

The risk in any sort of solubilization strategy is the propensity for precipitation upon administration and dilution into biological media. The presence of proteins and lipoproteins upon dilution can often facilitate supersaturation and allow for the time necessary to get further dilution and distribution in vivo. In essence, they often provide alternative equilibria for drug solubilization in vivo. The use of in vitro methods (94) and in vivo methods (95) to explore propensity for precipitation can often be very useful.

Solubility, coupled with dose and therapeutic indication, often define the ability to adequately deliver a drug parenterally. While the thermodynamic solubility ultimately dictates the actual chemical potential of the drug in solution under specified conditions, the total "solubilized drug" probably becomes the more relevant descriptor for drug delivery in parenteral systems. Efforts to solubilize drugs are highly dependent on altering either the conditions of the solvent system, creating alternative equilibria for the drug to reside in, changing the macroscopic solid form of the solute, or actually changing the solute at the molecular level (i.e., creating a new chemical entity). These alterations can increase the

escaping tendency from the solid state, facilitate the cavity formation in the solvent necessary for solute insertion, enhance the level of interactions between the solute and solvent, or simply provide an alternative state in which the molecule can reside. As will be discussed elsewhere in this book, the ultimate success of these strategies resides in the ability to deliver the molecule of interest to the in vivo milieu without deleterious results of precipitation upon administration.

## REFERENCES

1. Yalkowsky SH. Solubility and Solubilization in Aqueous Media. New York: Oxford University Press, 1999.
2. Martin AN, Swarbrick J, Cammarata A. Solubility and distribution phenomena. In: Martin AN, Swarbrick J, Cammarata A, eds. Physical Pharmacy. Philadelphia: Lee and Feriger, 1969.
3. Grant JWD, Higuchi T. Solubility Behavior of Organic Compounds. New York: Wiley Interscience, 1990.
4. Strickley RG. Solubilizing excipients in oral and injectable formulations. Pharm Res 2004; 21(2):201-230.
5. Singla AK, Garg A, Aggarwal D. Paclitaxel and its formulations. Int J Pharm 2002; 235(1-2):179-192.
6. Williamson KL. Macroscale and Microscale Organic Experiments. 2nd ed. Boston: Houghton Mifflin Co., 1994.
7. Lowry TH, Richardson KS. Mechanism and Theory in Organic Chemistry. 3rd ed. New York: Harper Collins Publishers, 1987:1090.
8. Tsierkezos NG, Filippou AC. Thermodynamic investigation of *N,N* dimethylformamide/toluene binary mixtures in the temperature range from 278.15 to 293.15K. J Chem Thermodyn 2006; 38(8):952-961.
9. Singh M. Surface tension and viscosity measurements of liquids with the survismeter: a single instrumental unit. Phys Chem Liq 2006; 44(5):579-584.
10. Gorman WG, Hall GD. Dielectric constant correlations with solubility and solubility parameters. J Pharm Sci 1964; 53:1017-1020.
11. Hildebrand JH, Scott RL. Phase equilibriums, chemical equilibriums, and solutions. In: Hildebrand JH, Scott RL, eds. The Solubility of Nonelectrolytes. 3rd ed. New York: Dover, 1964:488.
12. Hansen C, Beerbower A. Solubility parameters. Kirk Othmer Encycl Chem Technol, 2nd Ed. 1971; Suppl.:889-910.
13. Munafò A, Buchmann M, Nam Tran H, Kesselring UW. Determination of the total and partial cohesion parameters of lipophilic liquids by gas liquid chromatography and from molecular properties. J Pharm Sci 1988; 77(2):169-174.
14. Subrahmanyam CVS, Prakash KP, Rao PG. Estimation of the solubility parameter of trimethoprim by current methods. Pharm Acta Helv 1996; 71:175-183.
15. Adamson AW, Gast AP, eds. Physical Chemistry of Surfaces. 6th ed. New York: Wiley Interscience, 1997.
16. Kerber RC. If it's resonance, what is resonating? J Chem Educ 2006; 83(2):223-237.
17. Hansch C, Leo A, Hoekman D. Exploring QSAR: Fundamentals and Applications in Chemistry and Biology. Washington: American Chemical Society, 1995.
18. Anderson BD, Rytting JH, Higuchi T. Solubility of polar organic solutes in nonaqueous systems: role of specific interactions. J Pharm Sci 1980; 69(6):676-680.
19. Yan A, Gasteiger J. Prediction of aqueous solubility of organic compounds by topological descriptors. QSAR Comb Sci 2003; 22(8):821-829.
20. Saquing CD, Lucien FP, Foster NR. steric effects and preferential interactions in supercritical carbon dioxide. Ind Eng Chem Res 1998; 37(10):4190-4197.
21. Amidon GL, Yalkowsky SH, Anik ST, et al. Solubility of nonelectrolytes in polar solvents. V. Estimation of the solubility of aliphatic monofunctional compounds in water using a molecular surface area approach. J Phys Chem 1975; 79(21):2239-2246.
22. Valvani SC, Yalkowsky SH, Amidon GL. Solubility of nonelectrolytes in polar solvents. VI. Refinements in molecular surface area computations. J Phys Chem 1976; 80(8):829-835.
23. Hall LH, Kier LB, Murray WJ. Molecular connectivity. II: relationship to water solubility and boiling point. J Pharm Sci 1975; 64(12):1974-1977.
24. Yalkowsky SH, Banerjee S. Aqueous Solubility: Methods of Estimation for Organic Compounds. New York: Marcel Dekker Incorporated, 1992.
25. Hancock BC, Parks M. What is the true solubility advantage for amorphous pharmaceuticals? Pharm Res 2000; 17(4):397-404.
26. Sheffer E, Higuchi T. Dissolution behavior of crystalline solvated and nonsolvated forms of some pharmaceuticals. J Pharm Sci 1963; 52(8):781-791.
27. Ostwald W. Supposed isomerism of red and yellow mercuric oxide, and the surface tension of solid bodies. Zeit physikal Chem 1900; 34:495-503.

28. Freundlich H, ed. *Kolloidchemie*. Leipzig: Akademischer Verlagsgesellschaft, 1909.
29. Serajuddin ATM. Salt formation to improve solubility. *Adv Drug Delivery Rev* 2007; 59:603-616.
30. Dearden JC. In silico prediction of aqueous solubility. *Expert Opin Drug Discovery* 2006; 1(1):31-52.
31. Hopfinger AJ, Esposito EX, Llinas A, et al. Findings of the challenge to predict aqueous solubility. *J Chem Inf* 2009; 49(1):1-5.
32. Lipinski CA, Lombardo F, Dominy BW, et al. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv Drug Delivery Rev* 2001; 46(1-3):3-26.
33. Jain P, Sepassi K, Yalkowsky SH. Comparison of aqueous solubility estimation from aqueous functional group activity coefficients and the general solubility equation. *Int J Pharm* 2008; 360(1-2):122-147.
34. Ran Y, Yalkowsky SH. Prediction of drug solubility by the general solubility equation (GSE). *J Chem Inf Comput Sci* 2001; 41(2):354-357.
35. Delaney JS. ESOL: estimating aqueous solubility directly from molecular structure. *J Chem Inf Comput Sci* 2004; 44(3):1000-1005.
36. Myrdal P, Ward GH, Dannenfeller RM, et al. AQUAFAC 1: aqueous functional group activity coefficients; application to hydrocarbons. *Chemosphere* 1992; 24(8):1047-1061.
37. Bergstrom Christel AS, Wassvik Carola M, Norinder U, et al. Global and local computational models for aqueous solubility prediction of drug like molecules. *J Chem Inf Comput Sci* 2004; 44(4):1477-1488.
38. Hughes LD, Palmer DS, Nigsch F, et al. Why are some properties more difficult to predict than others? A study of QSPR models of solubility, melting point, and log P. *J Chem Inf Model* 2008; 48(1):220-232.
39. Johnson SR, Chen X Q, Murphy D, et al. A computational model for the prediction of aqueous solubility that includes crystal packing, intrinsic solubility, and ionization effects. *Mol Pharmaceutics* 2007; 4(4):513-523.
40. Anderson BD, Conradi RA. Predictive relationship in the water solubility of salts of a nonsteroidal anti-inflammatory drug. *J Pharm Sci* 1985; 74:815-820.
41. Ross DL, Riley CM. Aqueous solubility of some variously substituted quinolone antimicrobials. *Intern J Pharm* 1990; 63(3):237-250.
42. Childs SL, Stahly GP, Park A. The salt cocrystal continuum: the influence of crystal structure on ionization state. *Molecular Pharmaceutics* 2007; 4(3):323-338.
43. Wermuth C. Preparation of water soluble compound by covalent attachment of solubilizing moieties. In: Wermuth D, ed. *The Practice of Medicinal Chemistry*. 2nd ed. New York: Elsevier, 2003:617-630.
44. Stella VJ, Borchardt RT, Hageman MJ, et al. *Prodrugs: Challenges and Rewards*. New York: Springer, 2007.
45. Yalkowsky SH, Roseman TJ, eds. *Techniques of Solubilization of Drugs*. New York: Dekker, 1980.
46. Rubino JT. 'Cosolvents and Cosolvency' in *Encyclopedia of Pharmaceutical Technology*. New York: Informa Healthcare USA, Inc., 2007.
47. Tinwalla AY, Hoestery BL, Xiang TX, et al. Solubilization of thiazolobenzimidazole using a combination of pH adjustment and complexation with 2-hydroxypropyl- $\beta$ -cyclodextrin. *Pharm Res* 1993; 10(8):1136-1143.
48. Sanghvi R, Narazaki R, Machatha Stephen G, et al. Solubility improvement of drugs using *N*-methylpyrrolidone. *AAPS PharmSciTech* 2008; 9(2):366-376.
49. Rajewski RA, Stella VJ. Pharmaceutical applications of cyclodextrins. 2. *In Vivo Drug Delivery*. *J Pharm Sci* 1996; 85(11):1142-1169.
50. Ross DL, Riley CM. Physicochemical properties of the fluoroquinolone antimicrobials. III. Complexation of lomefloxacin with various metal ions and the effect of metal ion complexation on aqueous solubility. *Int J Pharm* 1992; 87(1-3):203-213.
51. Lee J, Lee SC, Acharya G, et al. Hydrotropic solubilization of paclitaxel: analysis of chemical structures for hydrotropic property. *Pharm Res* 2003; 20(7):1022-1030.
52. Saleh AM, El Khordagui LK. Hydrotropic agents: a new definition. *Int J Pharm* 1985; 24(2-3):231-238.
53. Higuchi T, Connors KA. Phase solubility techniques. *Advan Anal Chem Instr* 1965; 4:117-212.
54. Brewster ME, Loftsson T. Cyclodextrins as pharmaceutical solubilizers. *Adv Drug Delivery Rev* 2007; 59(7):645-666.
55. Stella VJ, Rao VM, Zannou EA, et al. Mechanisms of drug release from cyclodextrin complexes. *Adv Drug Delivery Rev* 1999; 36(1):3-16.
56. Loftsson T, Jarho P, Masson M, et al. Cyclodextrins in drug delivery. *Expert Opin Drug Delivery* 2005; 2(2):335-351.
57. Stella VJ, Rajewski RA. Cyclodextrins: their future in drug formulation and delivery. *Pharm Res* 1997; 14(5):556-567.
58. Connors KA. The stability of cyclodextrin complexes in solution. *Chem Rev (Washington, D C)* 1997; 97(5):1325-1357.

59. Loftsson T, Brewster ME. Pharmaceutical applications of cyclodextrins. 1. drug solubilization and stabilization. *J Pharm Sci* 1996; 85(10):1017 1025.
60. Lahiani Skiba M, Barbot C, Bounoure F, et al. Solubility and dissolution rate of progesterone cyclodextrin polymer systems. *Drug Dev Ind Pharm* 2006; 32(9):1043 1058.
61. Li P, Tabibi SE, Yalkowsky SH. Combined effect of complexation and pH on solubilization. *J Pharm Sci* 1998; 87(12):1535 1537.
62. Okimoto K, Rajewski RA, Uekama K, et al. The interaction of charged and uncharged drugs with neutral (HP b CD) and anionically charged (SBE7 b CD) b cyclodextrins. *Pharm Res* 1996; 13(2):256 264.
63. Sweetana S, Akers MJ. Solubility principles and practices for parenteral drug dosage form development. *PDA J Pharm Sci Technol* 1996; 50(5):330 342.
64. Paradis R, Page M. New active paclitaxel amino acids derivatives with improved water solubility. *Anticancer Res* 1998; 18(4A):2711 2716.
65. Bittner B, Gonzalez RCB, Walter I, et al. Impact of solutol HS 15 on the pharmacokinetic behaviour of colchicine upon intravenous administration to male wistar rats. *Biopharm Drug Dispos* 2003; 24(4):173 181.
66. Spornath A, Aserin A. Microemulsions as carriers for drugs and nutraceuticals. *Adv Colloid Interface Sci* 2006; 128 130:47 64.
67. Rane SS, Anderson BD. What determines drug solubility in lipid vehicles: is it predictable? *Adv Drug Delivery Rev* 2008; 60(6):638 656.
68. Burgess DJ, Ed. *Injectable Dispersed Systems: Formulation, Processing and Performance*. Boca Raton: Taylor and Francis, 2005.
69. Pouton CW. Self emulsifying drug delivery systems: assessment of the efficiency of emulsification. *Int J Pharm* 1985; 27(2 3):335 348.
70. von Corswant C, Thoren P, Engstroem S. Triglyceride based microemulsion for intravenous administration of sparingly soluble substances. *J Pharm Sci* 1998; 87(2):200 208.
71. Brime B, Moreno MA, Frutos G, et al. Amphotericin B in oil water lecithin based microemulsions: formulation and toxicity evaluation. *J Pharm Sci* 2002; 91(4):1178 1185.
72. Bello M, Colangelo D, Gasco MR, et al. Pertechnetate release from a water/oil microemulsion and an aqueous solution after subcutaneous injection in rabbits. *J Pharm Pharmacol* 1994; 46(6):508 510.
73. Bonacucina G, Cespi M, Misici Falzi M, et al. Colloidal soft matter as drug delivery system. *J Pharm Sci* 2009; 98(1):1 42.
74. Kipp JE. Solubilizing systems for parenteral formulation development small molecules. *Biotechnol Pharm Asp* 2007; 6(solvent systems and their selection in pharmaceuticals and biopharmaceuticals): 309 339.
75. Malcolmson C, Satra C, Kantaria S, et al. Effect of oil on the level of solubilization of testosterone propionate into nonionic oil in water microemulsions. *J Pharm Sci* 1998; 87(1):109 116.
76. Testard F, Zemb T, Strey R. Excess solubilization of lindane in bicontinuous microemulsions. *Prog Colloid Polym Sci* 1997; 105(Trends in Colloid and Interface Science XI):332 339.
77. Sottmann T. Solubilization efficiency boosting by amphiphilic block co polymers in microemulsions. *Curr Opin Colloid Interface Sci* 2002; 7(1,2):57 65.
78. Gasco MR. Microemulsions in the pharmaceutical field: perspectives and applications. *Surfactant Sci Ser* 1997; 66(industrial applications of microemulsions):97 122.
79. Li P, Ghosh A, Wagner RF, et al. Effect of combined use of nonionic surfactant on formation of oil in water microemulsions. *Int J Pharm* 2005; 288(1):27 34.
80. FDA. FDA: Draft guidance for industry: liposome drug products chemistry, manufacturing and controls, 2002.
81. O'Neil MJ, et al. *The Merck Index: an Encyclopedia of Chemicals, Drugs, and Biologicals*, Whitehouse Station, NJ: Merck Research Laboratories, 13th ed. 2001.
82. Yang T, Cui F D, Choi M K, et al. Liposome Formulation of paclitaxel with enhanced solubility and stability. *Drug Delivery* 2007; 14(5):301 308.
83. Gregoriadis G, Ed. *Liposome Technology: Liposome Preparation and Related Techniques*. New York: Informa Healthcare, 1993.
84. Basu SC, Basu M, Eds. *Liposome Methods and Protocols*. Totowa: Humana Press, 2002.
85. Mura P, Zerrouk N, Mennini N, et al. Development and characterization of naproxen chitosan solid systems with improved drug dissolution properties. *Eur J Pharm Sci* 2003; 19(1):67 75.
86. Cirri M, Maestrelli F, Corti G, et al. Simultaneous effect of cyclodextrin complexation, pH, and hydrophilic polymers on naproxen solubilization. *J Pharm Biomed Anal* 2006; 42(1):126 131.
87. Li P, Tabibi SE, Yalkowsky SH. Solubilization of flavopiridol by pH control combined with cosolvents, surfactants, or complexants. *J Pharm Sci* 1999; 88(9):945 947.
88. Loftsson T, Fridriksdottir H, Sigurdardottir AM, et al. The effect of water soluble polymers on drug cyclodextrin complexation. *Int J Pharm* 1994; 110(2):169 177.

89. Pitha J, Hoshino T. Effects of ethanol on formation of inclusion complexes of hydroxypropyl cyclodextrins with testosterone or with methyl orange. *Int J Pharm* 1992; 80(2-3):243-251.
90. Liu R, Ed. *Water Insoluble Drug Formulation*. Boca Raton: CRC Press, 2000.
91. Usui F, Maeda K, Kusai A, et al. Inhibitory effects of water soluble polymers on precipitation of RS 8359. *Int J Pharm* 1997; 154(1):59-66.
92. Malmsten M. *Surfactants and Polymers in Drug Delivery*. New York: Marcel Dekker, 2002.
93. Ribeiro L, Carvalho RA, Ferreira DC, et al. Multicomponent complex formation between vinpocetine, cyclodextrins, tartaric acid and water soluble polymers monitored by NMR and solubility studies. *Eur J Pharm Sci* 2005; 24(1):1-13.
94. Cox JW, Sage GP, Wynalda MA, et al. Plasma compatibility of injectables: comparison of intravenous U 74006F, a 21 aminosteroid antioxidant, with dilantin brand of injectable phenytoin. *J Pharm Sci* 1991; 80:371-375.
95. Davio SR, McShane MM, Kakuk TJ, et al. Precipitation of the renin inhibitor Ditekiren upon IV infusion; in vitro studies and their relationship to in vivo precipitation in the cynomolgus monkey. *Pharm Res* 1991; 8(1):80-83.



# 7 | Formulation of depot delivery systems

James J. Cunningham, Marc J. Kirchmeier, and Sachin Mittal

## INTRODUCTION AND DRIVERS FOR DEPOT DELIVERY

Depot delivery systems, also known as sustained-release systems, are parenteral formulations containing multiple doses of drug that, when introduced into the body, are designed to release the drug over a specified, often prolonged, period of time. Depot formulations come in many forms, designed for several different administration routes, and have been in use for over half a century. In addition to the many depot pharmaceuticals approved for use today, the development of novel systems remains an active area of research because of the ability of depot systems to overcome several well-recognized challenges often associated with conventional delivery. These include variations in drug plasma levels between doses that can lead to adverse effects or compromised efficacy, poor patient compliance due to frequent dosing, and difficulty localizing exposures to the target organ or tissue.

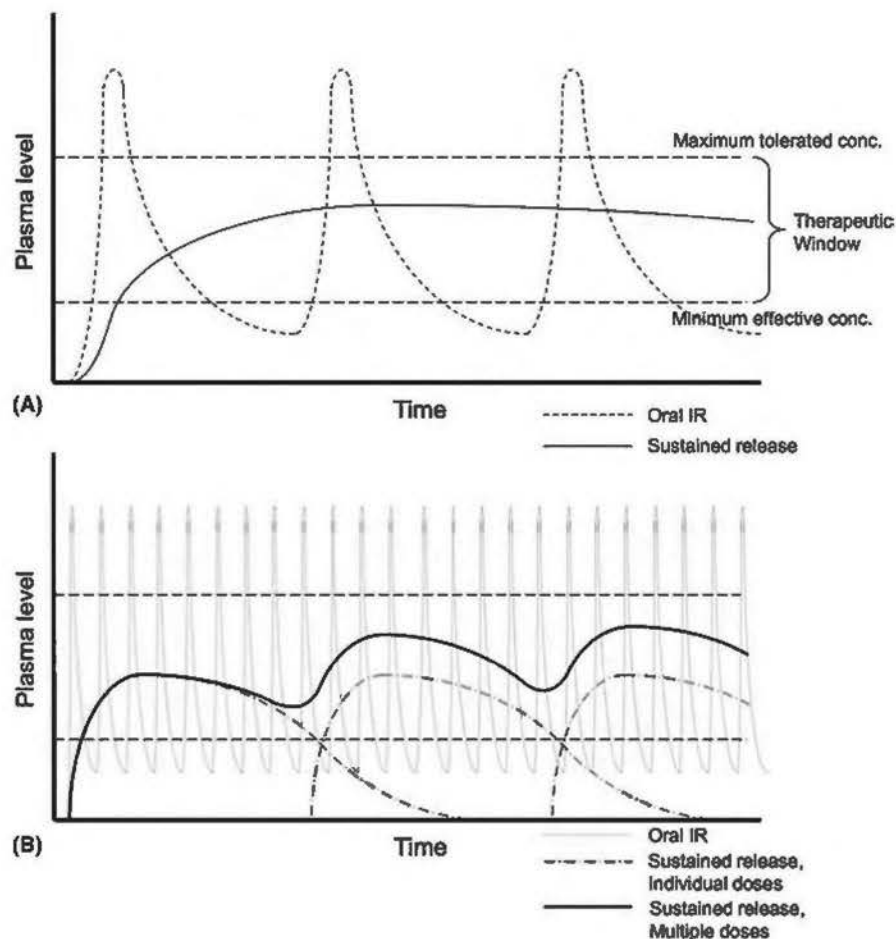
### Advantages of Depot Delivery Systems

As earlier chapters in this book have highlighted, parenteral drug delivery can overcome many of the challenges associated with oral delivery of bioactive molecules, including degradation in the gut, low permeation through intestinal mucosa, and high first pass metabolism. It is generally recognized that, for certain therapeutic molecules, such as proteins, parenteral dosing is indeed often the only viable way to deliver pharmacologically relevant doses. At the same time, relative to other routes of administration, injection is invasive and is generally less preferred as a means of administering therapeutics. Depot delivery systems provide one way to mitigate this issue by decreasing the frequency of administration. For example, BYDUREON™, pending FDA approval for the treatment of type II diabetes, promises to reduce the frequency of dosing from twice daily with the current product, BYETTA™, to once weekly with the depot formulation (1).

Certain classes of drugs have relatively narrow therapeutic windows, defined as the concentration in vivo above which a compound is therapeutically effective, but below that at which toxic effects are observed (2). For these drugs, it can be challenging to maintain plasma concentrations within the therapeutic window (Fig. 1). In some cases, such as when the molecule has a very short half life, and is not well absorbed along the length of the GI tract, oral dosing may simply not be feasible. The gold standard for maintaining precise control over plasma drug levels is continuous infusion, typically via the intravenous route (3). Clearly, despite the degree of control it offers, continuous IV infusion is often not practical because of heightened risk and the need for close medical supervision during treatment. Depot delivery systems can avoid the peaks and troughs in plasma concentrations common with conventional dosing, and maintain the plasma concentration within the therapeutic window, by providing an infusion-like profile without the drawbacks of IV delivery.

In some cases, such as cancer treatment, it may be desirable to limit drug exposure to the site of action, and minimize systemic exposure altogether. The GLIADEL® wafer, a depot formulation of carmustine, which is implanted at the surgical site after brain tumor resection, is one example of this approach (4). Intra-articular injection of corticosteroid depots is another example where local effects at the site of action can be maximized relative to systemic effects (5).

Poor compliance is increasingly recognized as a significant factor in the failure of therapy in certain patients and there is an inverse relationship between dose frequency and compliance (6). Schizophrenia is one such example, where compliance rates are estimated at about 50% (7). Depot formulations of antipsychotics were first introduced in the early 1960s, initially for patients with suicidal or violent tendencies, but later became well-accepted as maintenance therapies (7,8). Depot antipsychotics are also reported to reduce the frequency of side effects



**Figure 1** (A) An idealized representation of plasma concentration versus time obtained following oral dosing and administration of a sustained release formulation. Note that oral dosing can result in large variations in plasma concentrations between doses, and that plasma concentrations may not be maintained within the therapeutic window. In contrast, sustained release formulations are capable of maintaining relatively constant plasma profiles over time. (B) Plasma concentration versus time profiles for oral and multiple sustained release doses over a longer period of time.

(7). RISPERDAL<sup>®</sup> CONSTA<sup>®</sup> was the first atypical antipsychotic approved as an injectable depot. As evidence of its impact, sales have grown to \$870 million (IMS, 2006).

Despite their many advantages, there are some drawbacks to depot delivery, including difficulty in removing the dose once administered, lack of dosing flexibility, the need for injection or implantation, and potential local adverse tissue reactions (9). These limitations can, in many cases, be managed or overcome. In cases where it is necessary to maintain the ability to cease dosing, nondegradable implant systems can be utilized. Several products, such as Lupron Depot<sup>®</sup>, include formulations that release for varying periods of time to improve dosing flexibility. Most modern sustained-release formulations can be delivered through conventional needles (although admittedly large-bore by current standards), and the excipients used in the formulations are generally nonirritating. The properties of an ideal depot delivery system include extent and duration of release matched to the needs of the

Downloaded from informahealthcare.com by McGill University on 01/15/13  
For personal use only

indication, tolerability and lack of toxicity, and biodegradability (in most cases). Zero order release is often desired, although this can be difficult to achieve in practice, and many products have been commercialized without meeting this criterion. The ability to alter the release rate during administration, while not currently possible in commercialized systems, would also be a desirable option, and is an active area of research.

### History and Types of Depot Formulations

Depot formulations have been in use for well over half a century; implantation of testosterone pellets was employed in the 1930s (10). The first widely marketed depot formulations, launched in the 1950s, were injectable intramuscular (IM) suspensions of drugs in aqueous and oily vehicles. A number of additional suspension and oily-vehicle depot formulations, based on poorly soluble alkane ester prodrugs, were developed and launched during the 1960s and 1970s. Use of the biodegradable polyester, poly(lactic-co-glycolic acid) (PLGA), for drug delivery began in the 1970s (11), culminating in the U.S. launch of the PLGA microsphere product, Lupron Depot<sup>®</sup>, in 1989. In the years following, a number of additional PLGA depot products were launched, including a microsphere formulation of a protein, and extruded PLGA rods. The 1990s saw the introduction of new polymers and lipid-based strategies for sustained-release delivery, as well as the development of implantable device-based depot systems. These strategies have enabled a number of product launches that have continued into recent years.

### Requirements for Pharmaceutical Actives Suitable for Depot Delivery

Given the practical constraints and technical challenges associated with developing parenteral sustained-release formulations, pharmaceutical actives must meet certain requirements to be suitable for depot delivery. These requirements vary according to the specific depot strategy selected, but several criteria are general. Most importantly, actives should be potent to allow incorporation of the entire quantity of active needed for dosing over the lifetime of the depot, at a reasonable drug loading within the system. The required potency should be estimated by considering the desired duration of release, and injection volume and drug loading constraints. Note that, when oral PK/PD data exist, it is important to consider the impact that parenteral dosing may have on exposures; this often works to the advantage of the formulator in terms of reduced doses because of absorption limitations and first pass metabolism via oral dosing. Stability is the second criterion, as it is necessary to ensure that the active remains stable not only during the manufacturing process and over the shelf life of the product, but also after administration, within the environment of the body. Stability at body temperature, in an aqueous environment, and in the presence of proteins and enzymes, may become important considerations. Solubility, in aqueous media, solvents that may be used in the manufacturing process, and within the formulation itself, is the third important criterion. Specific solubility requirements will vary according to the formulation approach, and may indeed dictate the formulation strategy. Additional criteria include PK/PD profile (therapeutic window), lack of irritation of the active to local tissues, and the absorption profile of the active. In determining the suitability of an active for depot delivery, it is also important to consider the requirements of the therapeutic area. Therapeutic areas that require extended periods of dosing, high compliance rates, and localized delivery lend themselves to depot formulations. Specific examples of relevant therapeutic areas include hormone therapy (testosterone, estrogen, GnRH antagonists, etc.), corticosteroid treatment, basal insulin delivery, antipsychotics, and contraception.

### SUSPENSION AND OILY-VEHICLE DEPOT SYSTEMS

Formulations based on suspensions of drug substance in aqueous or oily vehicles were amongst the first long-acting injectable delivery systems developed (Table 1). These systems rely in large part on the dissolution properties of the suspension particles to govern the release rate from the depot. When the solubility of the drug substance in an oily vehicle allows, an alternate approach is to formulate an oil solution of the drug; in this case the formulator relies

**Table 1** A Partial List of Injectable Suspension and Oily Vehicle Sustained Release Products Approved in the United States

Trade name	Active	U.S. approval	Excipients (reference number)
Aristocort	Triamcinolone diacetate, 40 mg/mL	1961, Fujisawa	PEG 3350, 3% Tween 80, 0.2% Sodium chloride, 8.5 mg/mL Benzyl alcohol, 9 mg/mL pH ~6 (12)
Aristospan	Triamcinolone hexacetonide, 5, 20 mg/mL	1969, Fujisawa	Sorbitol, 50% Polysorbate 80, 0.2 0.4% Benzyl alcohol, 0.9% pH 4.5 6.5
Bicillin C R	Penicillin G Benzathine, 300,000 U/mL, Penicillin G Procaine, 300,000 U/mL	1953, Wyeth Ayerst	CMC, 0.55% Lecithin, 0.5% Povidone, 0.1% Methylparaben, 0.1% Propylparaben, 0.01% Sodium citrate pH 6 8.5 (12)
Bicillin L A	Penicillin G Benzathine, 600,000, 300,000 U/mL	1958, Wyeth Ayerst	Lecithin, 0.5% CMC, 0.6% Povidone, 0.6% Methylparaben, 0.1% Propylparaben, 0.01% Sodium citrate buffer
Celestone Soluspan	$\beta$ methasone sodium phosphate / acetate, 3 mg/mL	1965, Schering	Sodium phosphate dibasic, 7.1 mg/mL Sodium phosphate monobasic, 3.4 mg/mL EDTA, 0.1 mg/mL Benzalkonium chloride, 0.2 mg/mL pH 6.8 7.2 (12)
Cortone	Cortisone acetate, multiple strengths	1950	Sodium CMC, 5 mg/mL Tween 80, 4 mg/mL Sodium chloride, 9 mg/mL Benzyl alcohol, 9 mg/mL (12)
Decadron LA	Dexamethasone acetate, 8 mg/mL	1973	Sodium CMC, 5 mg/mL Tween 80, 0.75 mg/mL Sodium chloride, 6.7 mg/mL Creatinine, 5 mg/mL EDTA, 0.5 mg/mL Benzyl alcohol, 9 mg/mL Sodium bisulfite, 1 mg/mL pH 5.0 7.5 (12)
Deca durabolin	Nandrolone decanoate, 25, 50 mg	1962, Organon	Arachis oil Benzyl alcohol, 10%
Delalutin	Hydroxyprogesterone caproate, 125, 250 mg/mL		Castor oil Benzyl benzoate Benzyl alcohol (13)
Delatestryl	Testosterone enanthate, 200 mg/mL	1953, Squibb	Sesame oil Chlorobutanol, 5 mg/mL (12)
Delestrogen	Estradiol valerate, 10, 20, 40 mg/mL	1954, Squibb	Castor oil Benzyl benzoate Benzyl alcohol Ethanol (13) Sesame oil
Depinar	Cyanocobalamin Zn tannate	1980, Armour	Aluminum monostearate, 2% (14)
Depo Estradiol	Estradiol cypionate, 5 mg/mL	1979, Upjohn	Cottonseed oil Chlorobutanol anhydrous, 5.4 mg/mL
Depo Medrol	Methylprednisone acetate, 20, 40, 80 mg/mL	1959, Upjohn	PEG 3350, 3% Tween 80, 2 mg/mL Sodium phosphates, 2 mg/mL Benzyl alcohol 9 mg/mL Sodium chloride (isotonic) pH 3.5 7.0 (12)

(continued)

Downloaded from informahealthcare.com by McGill University on 01/15/13  
For personal use only

**Table 1** A Partial List of Injectable Suspension and Oily Vehicle Sustained Release Products Approved in the United States (*continued*)

Trade name	Active	U.S. approval	Excipients (reference number)
Depo Provera	Medroxyprogesterone (progesterone), acetate, 100, 400 mg/mL	1960, Upjohn	PEG 3350, 20 29 mg/mL Tween 80, 2.4 mg/mL Sodium chloride, 8.7 mg/mL Methylparaben, 1.4 mg/mL Propylparaben, 0.15 mg/mL (12)
Depo Sub Q Provera 104	Medroxyprogesterone acetate, 104 mg	2004, Pharmacia and Upjohn	PEG Polysorbate 80 Povidone Monobasic sodium phosphate Dibasic sodium phosphate Methionine Sodium chloride Parabens
Depo testadiol	Estradiol cypionate, 2 mg/mL, testosterone cypionate, 50 mg/mL	1980, Upjohn	Cottonseed oil Chlorobutanol anhydrous, 5.4 mg/mL
Depo testosterone	Testosterone cypionate, 200 mg	1979, Upjohn	Cottonseed oil (15)
Ditate DS	Testosterone enanthate, 180 mg/mL, estradiol valerate, 8 mg/mL	1982, Savage	Ethyl oleate BP (15)
Haldol	Haloperidol decanoate, 50, 100 mg	1986	Sesame oil Benzyl alcohol, 1.2% (12)
HP Acthar	ACTH Zn tannate	1952, Armour	Gelatin, 16% Phenol, 0.5% (16)
Hydeltra TBA	Prednisolone Tebutate, 20 mg/mL	1956	Sorbitol Polysorbate 80 Sodium citrate
Hydro cortone	Hydrocortisone acetate, 50 mg/mL	1951	Benzyl alcohol (17) Sodium CMC, 5 mg/mL Tween 80, 4 mg/mL Sodium chloride, 9 mg/mL Benzyl alcohol, 9 mg/mL (12)
Kenalog 10, 40	Triamcinolone acetonide, 10, 40 mg/mL	1960	Sodium CMC Polysorbate 80 Sodium chloride Benzyl alcohol (17)
Lantus	Insulin glargine, 100 U/mL	2000, Sanofi Aventis	Glycerol 85% M cresol Polysorbate 20 Zinc
Lunelle	Medroxyprogesterone acetate, 25 mg Estradiol cypionate, 5 mg	2000, Pharmacia and Upjohn	PEG, 28.56 mg/mL Polysorbate 80, 1.9 mg/mL Methylparaben, 1.8 mg/mL Propylparaben, 0.2 mg/mL Sodium chloride, 8.56 mg/mL
Percorten	Desoxycortisone pivalate, 25 mg/mL	Ciba	Methylcellulose Sodium CMC Polysorbate 80 Sodium chloride Thimerosal (17)
Plenaxis	Abarelix, 100 mg	2003, Praecis	CMC Reconstituted in sodium chloride
Prolixin Decanoate, 25 mg/mL	Fluphenazine decanoate	1972, Squibb	Sesame oil Benzyl alcohol, 1.2%
Prolixin Enanthate, 25 mg/mL	Fluphenazine enanthate	1967, Squibb	Sesame oil Benzyl alcohol

**Table 1** (continued)

Trade name	Active	U.S. approval	Excipients (reference number)
Sus phrine	Epinephrine HCl, 5 mg/mL	1951	Glycerin, 325 mg/mL Thioglycolic acid, 6.6 mg/mL Ascorbic acid, 10 mg/mL Phenol, 5 mg/mL (12)

Note: Note that some of these products have been discontinued. Approval dates were referenced from Drugs@FDA ([http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Search Drug Name](http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Search%20Drug%20Name)).

Abbreviation: CMC, carboxymethylcellulose.

chiefly on the oil/water partition coefficient and dispersion of the vehicle to govern release. We will discuss both approaches in more detail in this section. A third approach is adsorption of the active component to a solid adsorbent (3); this approach is commonly used in vaccine formulations, but will not be discussed in more detail here. Suspension and oily-vehicle formulations are generally suitable only for compounds with low aqueous solubility. If the aqueous solubility of the drug substance is too high to enable formulation by these approaches, solubility can be reduced by formation of a poorly soluble prodrug. One common approach is esterification with alkanes (e.g., to form enanthates, decanoates, or cypionates), an approach used extensively for hormones such as testosterone (3). Alternatively, poorly soluble complexes or salts can be formed, such as zinc-insulin and carboxymethylcellulose (CMC) complexes (3). Suspension and oily-vehicle depot formulations are most often administered by the IM route, although they can also be administered via the subcutaneous (SC), intra-articular, and intradermal routes.

### Physical Stability of Suspensions

Injectable suspensions are dispersions of solid drug in an aqueous or oily liquid vehicle. The most common are coarse suspensions, which typically have a mean particle size of less than about 50  $\mu\text{m}$  to ensure that they can be administered through a suitably sized hypodermic needle, and to slow the rate of settling (18). The rate of settling of particles in a dispersion is governed by Stokes' law.

$$v = \frac{\Delta\rho g d^2}{18\eta}$$

where  $v$  is the velocity of sedimentation,  $\Delta\rho$  is the density difference between the phases,  $g$  is the gravitational acceleration,  $d$  is the particle radius, and  $\eta$  is the viscosity of the continuous phase (18). Given the goal of slowing the sedimentation rate, Stokes' law instructs the formulator to decrease the particle size and density difference between the phases, and increase the viscosity of the continuous phase. We will later examine how excipients can be used to accomplish these goals.

Stokes' law assumes uniform and noninteracting particles. In reality, interactions between suspended particles are significant and include attractive van der Waals forces, and repulsive electrical double layer and solvation/hydration forces (19). One of the primary failure modes in the formulation of suspensions is caking, which results from the settling of particles and the formation of a densely-packed layer of solids (17). The distance between particles is sufficiently decreased within the cake so that attractive van der Waals forces dominate and cause irreversible aggregation of the particles, preventing their redispersion. One technique used to prevent caking is to formulate the suspension to flocculate. Flocculated particles interact to form a loosely aggregated structure, where interparticle distances are sufficiently large that the system is easily resuspended (e.g., by brief shaking). Formulation at the secondary minimum of the potential energy function can maximize the stability of the flocculated system (18).

A second failure mode, particularly in nanoparticulate systems, is particle growth over time through Ostwald ripening. This phenomenon is described by the Ostwald-Freundlich equation.

$$\ln \frac{C_1}{C_2} = \frac{2M\gamma}{\rho RT} \left( \frac{1}{r_1} - \frac{1}{r_2} \right)$$

where  $C_1$  and  $C_2$  are the saturation solubility at the surface of particles of radius  $r_1$  and  $r_2$ , respectively.  $M$  is molecular weight,  $\gamma$  is the surface energy of the solid in contact with the solution,  $\rho$  is the density of the solid,  $R$  is the gas constant, and  $T$  is absolute temperature (17). The phenomenon is driven by the higher saturation solubility at the surface of small particles relative to larger ones, as a result of curvature effects. Drug therefore dissolves from the surface of small particles, diffuses to the vicinity of larger particles where saturation solubility is exceeded, and deposits on to the surface of the larger particles, causing a net upward shift in particle size of the system. It must always be appreciated that micro- and nanosuspension systems are thermodynamically unfavorable, and that one must rely on slowing the kinetics to ensure physical stability of these formulations.

#### Formulation of Parenteral Suspensions

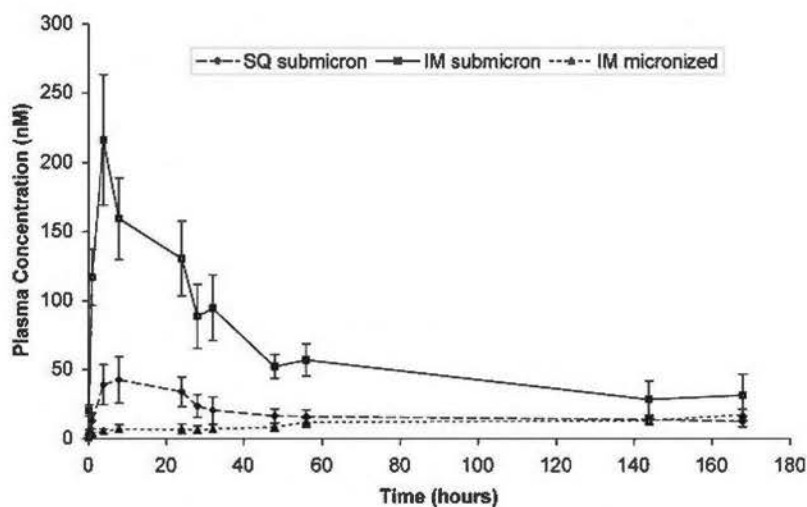
The ideal parenteral suspension is easily resuspended with mild shaking and does not cake upon storage, does not settle rapidly and remains homogenous long enough to allow reproducible dosing, maintains stability and elegance over its shelf life, maintains sterility during storage and use, and is easily administered through a 20- to 25-gauge needle (17). Like all formulations, the formulation of injectable suspensions should begin with a thorough preformulation characterization including solubility in water over a range of pH and in the presence of stabilizing surfactants and polymers, chemical stability in both solid state and solution, and full characterization of drug forms including polymorphs, hydrates and solvates. Drug form can significantly influence the rate of absorption from the injection site (20). After IM administration, aqueous suspensions tend to form a loose agglomerate within the fibrous or membranous tissues between muscle fibers, while the vehicle is rapidly absorbed (21).

#### Particle Size

Drug particle size can have a significant impact on formulation physical stability, syringeability, and release rate, and therefore should be well characterized and controlled through approaches such as controlled crystallization or milling (17). It is important that the process used provide a narrow particle size distribution to minimize Ostwald ripening, and that the potential for form change, for example, to the amorphous form, be well-understood given the potential adverse impact on physical stability (22). Particle size reduction techniques include jet milling, spray drying, and supercritical fluid processing (18). Wet media milling can be used to generate nanocrystalline dispersions (23): the Elan NanoCrystal<sup>®</sup> technology is used in Janssen's product INVEGA SUSTENNA<sup>™</sup>. Compared with coarse suspensions, reduction of particle size to the submicron range enhances physical stability (reduced settling rate), homogeneity, syringeability (reduced viscosity), and options for sterilization (23).

Particle size has a significant effect on syringeability, and it is critical to evaluate suspension systems for syringeability and injectability. A typical recommendation to prevent particle "bridging" that could lead to clogging, is to limit the size of the largest particles to no larger than one-quarter to one-third the inner diameter of the needle (17). The viscosity of the formulation should be optimized to ensure a balance between physical stability of the suspension and syringeability. Thixotropy and shear-thinning behavior can be leveraged to accomplish both goals, as in the case of penicillin G procaine suspensions (24).

The impact of particle size on release rate and pharmacokinetics has been the subject of a number of published studies. Procaine penicillin G aqueous IM suspensions demonstrated faster release as particle size was reduced from 60 to 100 mesh to micronized size (25). The trend was similar for oil suspensions, unless the system was gelled by addition of aluminum monostearate, in which case the trend was reversed. In a separate study, in which aqueous



**Figure 2** Mean plasma concentration versus time profiles for a poorly soluble Merck compound after subcutaneous or intramuscular administration to rats of coarse or submicron drug suspension formulations. The composition of the suspension vehicle was the same for both suspensions, as was the dose (20 mg/kg). Data are mean  $\pm$  SE,  $n = 3-4$ ).

phenobarbital suspensions were administered intramuscularly to dogs, the area under the blood level curve was found to decrease as particle size increased from 6.63 to 29.96  $\mu\text{m}$  (26). Studies of IM aqueous suspensions of model compounds in rats also demonstrated that the absorption rate constant increased with decreasing particle size (21). This effect was particularly apparent as particle size was decreased to 2 to 3  $\mu\text{m}$  or smaller, possibly because of the ability of smaller particles to migrate more easily through the fibrous tissues at the injection site, enabling the depot to spread further following injection. In studies performed in our laboratories on aqueous suspension formulations of a poorly soluble drug, we similarly observed that reduction of particle size led to much faster absorption from a submicron suspension as compared with a coarse suspension (Fig. 2), by IM dosing. We also observed much faster absorption of the submicron suspension when administered by the IM route, compared with the SC route, highlighting the importance of administration route.

Theoretically, the release rate of drug from the depot under sink conditions is given by the following equation:

$$\left(\frac{Q}{t}\right)_d = \frac{S_a D_s C_s}{\delta_s}$$

where  $Q$  is the amount of drug released in time  $t$ .  $S_a$  is the surface area of drug in contact with the surrounding fluid,  $D_s$  is the diffusion coefficient of drug molecules in the fluid,  $C_s$  is the saturation solubility of the drug, and  $\delta_s$  is the thickness of the hydrodynamic diffusion layer surrounding the solid (3). The faster dissolution of smaller particles is explained by their higher surface area, but this relationship is only relevant if the particles remain at least partially dispersed after administration, as demonstrated by the results of the gelled oil system referenced previously.

#### Excipients

Earlier in this section we discussed the use of excipients to aid in the stabilization of suspensions. Nonionic surfactants, such as polysorbate 80, are commonly used to wet and sterically stabilize the drug particle surface (18). Povidone and lecithin have been used less



commonly for this purpose (17). Polymers such as CMC and high molecular weight polyethylene glycol (e.g., PEG 3350) are commonly used to increase the viscosity of the continuous phase. Additional excipients may include buffers, antimicrobial preservatives, and electrolytes such as sodium chloride. The latter may be used both to ensure tonicity, and to adjust ionic strength to impact flocculation (18). The total solids content in parenteral suspensions is often limited by the syringeability and injectability of the system, and may impose an upper limit on drug concentration.

#### *Manufacture and Control of Parenteral Suspensions*

Suspension formulations can be very challenging to develop and manufacture. They can be prepared either as ready to use suspensions, or as powders for reconstitution. It is typically not possible to sterilize suspension systems by sterile filtration, so they must either be manufactured under aseptic conditions, or terminally sterilized by heat or ionizing radiation. Two processes used to prepare parenteral suspensions are aseptic combination of sterile powder and vehicle, and in situ crystallization from sterile solutions (17). For the latter, sterile powder can be prepared by aseptic antisolvent crystallization, lyophilization, or spray drying (17). Particle size reduction is often required and can be accomplished by milling, and the vehicle is typically sterilized by either filtration or heat sterilization (17). Additional manufacturing considerations include entrapped air and foam, and particulate matter control (17).

#### **Oily-Vehicle Solution Depot Systems**

Compounds with low solubility, poor stability, or the potential for causing irritation in aqueous vehicles can be formulated as injectable solutions in oily vehicles. Advantages of this approach relative to suspension formulations include greater ease of manufacture, fewer physical stability concerns, and the ability to sterilize by filtration. Clearly, for this approach to be viable, the active must be sufficiently soluble and stable in the selected vehicle. As for suspensions, hydrophilic compounds can be converted to lipophilic prodrugs for formulation as a depot.

Ideally, oils for use in depot formulations should be chemically stable and inert to reactions with the drug, relatively low in viscosity, physically stable across a wide range of temperature, nonirritating, and free of antigenic properties (27). Oils acceptable for injection include fixed oils such as olive oil, corn oil, sesame oil, arachis oil, almond oil, peanut oil, poppyseed oil, soybean oil, cottonseed oil, and castor oil (28). Vegetable oils, as natural products, contain a variety of triglyceride components, including olein, linolein, stearin, palmitin, and myristin (29). Sesame oil is generally preferred because of its enhanced stability, imparted by natural antioxidants, however, it is light-sensitive (28). Isopropyl myristate, ethyl oleate, benzyl benzoate, polyoxyethylene oleic triglycerides (Labrafils), thin vegetable oil (fractionated coconut oil, Viscoleo) and PEGs are synthetic alternatives (28). Ethyl oleate is sometimes preferred because of lower viscosity. The fixed oils are generally well-tolerated, however, some patients may have allergic reactions to vegetable oils (28). Oily depots are typically administered intramuscularly, as SC injection has resulted in pain and irritation at the injection site (28).

Many oily vehicles are eliminated from the injection site slowly, by dissolution in body fluids or conversion to soluble species, or via the shedding and transport of oil microdroplets from the depot surface (29). Visual observation after IM administration has indicated that oil depots do not spread as extensively as aqueous systems and take on a flattened, pod-like shape (29). This is important because the surface area of the depot is expected to be a key determinant of release rate. The absorption of drugs from oil solutions has been shown to obey first-order kinetics in cases when the absorption of the vehicle is slow relative to the active. In this case, diffusion of the active through the aqueous phase surrounding the depot is rate limiting, and the rate constant is controlled by both the oil/water partition coefficient and the vehicle injection volume. By contrast, the absorption of drugs from oily suspensions can obey zero order kinetics, since the solubility of the drug in the vehicle is maintained at the saturation solubility until the suspension particles have completely dissolved (29).

**DEGRADABLE POLYMERIC DEPOT DELIVERY SYSTEMS****Poly(Lactide-co-Glycolide) Systems**

Polyesters of poly(lactic acid) (PLA) and copolymers of lactic and glycolic acids, referred to as PLGA, are the most commonly used polymers in biodegradable depot dosage forms. These biocompatible polymers undergo random, mostly nonenzymatic, ester linkage hydrolysis to form lactic acid and glycolic acid, which are normal metabolic compounds in the body. Resorbable sutures, clips and implants were the earliest applications of these polymers (30). The application of PLA and PLGA as biodegradable and biocompatible polymers for drug delivery was initiated in the 1970s (11,31,32). Southern Research Institute developed the first synthetic, resorbable suture (Dexon<sup>®</sup>) in 1970, and the first patent describing the use of PLGA polymers in a sustained-release dosage form appeared in 1973 (33).

PLGA is synthesized by means of a random ring-opening copolymerization of two different monomers, the cyclic dimers of glycolic acid and lactic acid. Thus, the polymers or copolymers may be produced by the polycondensation of the lactic acid and/or glycolic acid in the presence of an inorganic acid (34). Today, PLGA polymers are commercially available from multiple suppliers, including Boehringer-Ingelheim (Resomer<sup>®</sup>), PURAC (Purasorb<sup>®</sup>), Absorbable Polymers International (Lactel<sup>®</sup>), and Alkermes (Medisorb<sup>®</sup>). PLGA polymers are available commercially as end capped or acid terminated and with inherent viscosities ranging from 0.15 to 6.5 dL/g (35).

*Polymer Selection and Degradation*

Understanding the physicochemical and biological properties of a polymer is important prior to selection of a polymer for depot drug delivery. PLGA polymer can generally be characterized by molecular weight (inherent viscosity), polydispersity, lactide to glycolide ratio, and chemistry (end capped vs. acid terminated). The selection of the polymer for depot delivery would depend on the target release profile of the drug, with the drug release mainly governed by the degradation of the polymer. A vast amount of literature is available on the characterization of PLGA, its biodegradation, and drug release properties. The polymer PLA exists in an optically active (L-PLA; semicrystalline) and an optically inactive (DL-PLA; amorphous) form. The amorphous form is preferred, as it enables a more homogenous dispersion of the drug in the polymer matrix (36). The glass transition temperature of the DL-PLA and PLGA is about 30°C to 60°C and is represented by the following equation:

$$T_g = T_g^0 + \frac{K}{M_n}$$

where  $T_g^0$  (60.1°C for PLA) is a limiting  $T_g$  of a material of infinite MW,  $M_n$  is a number average MW, and  $K$  ( $37.1 \times 10^4$  °C for PLA) is a constant for the polymer (37,38).

Lactic acid is more hydrophobic than glycolic acid and hence, PLGA polymers rich in lactic acid are more hydrophobic, absorb less water, and degrade at a slower rate (31,39 41). Generally, a bulk erosion mechanism (a homogenous chain cleavage reaction throughout the matrix) has been considered as the main degradation pathway for PLA and PLGA (42,43). However, recent studies on the degradation of various PLGA copolymers have demonstrated a heterogeneous degradation mechanism. The degradation products generated in the interior autocatalytically accelerate the degradation process, because of an increased amount of carboxylic acid end groups and thus, a decrease in the microclimate pH (43 45). Enzyme catalyzed degradation has been hypothesized, but these studies are not convincing (46). The factors that can influence the hydrolytic degradation of lactide/glycolide homopolymer and copolymer include: water permeability and solubility (hydrophilicity/hydrophobicity), chemical composition, mechanism of hydrolysis (noncatalytic, autocatalytic, enzymatic), additives (acidic, basic, monomers, solvents, drugs), morphology (crystalline, amorphous), device dimensions (size, shape, surface to volume ratio), porosity, glass transition temperature (glassy, rubbery), molecular weight and molecular weight distribution, physicochemical factors (ion exchange, ionic strength, pH), sterilization, and site of implantation (47). The kinetics of biodegradation of PLGA microspheres were studied in rats using steroid microspheres prepared with radiolabeled PLGA of varying composition (48 50). The

degradation of PLGA ranged from 10 weeks (50:50 lactide to glycolide) to approximately 30 weeks (87:13 lactide to glycolide), and finally to 45 weeks with 100% lactide (49). PLGA has found application in multiple depot products in the market. Some of the marketed PLGA based depots are summarized in Table 2.

#### *PLGA Microspheres*

PLGA microspheres are by far the most commonly used polymer-based injectable depot drug delivery systems, and are advantageous for several reasons. PLGA microspheres are biocompatible, can be easily administered through a syringe, can provide sustained release for prolonged periods of time, and can encapsulate active molecules with wide-ranging physicochemical properties, including small molecules, peptides, proteins and nucleic acids (51).

A number of techniques have been developed for the microencapsulation of drugs, such as solvent evaporation and solvent extraction [oil-in-water (o/w) emulsion, water-in-oil-in-water (w/o/w) emulsion, and solid-in-oil-in-water (s/o/w) emulsion], phase separation or coacervation, spray drying, extrusion, and supercritical fluid based encapsulation. Although each process is associated with certain advantages and disadvantages, in general, the selection of the microencapsulation process is dependent on the nature of the polymer, the drug, the intended use, and duration of therapy (36,41,45-54). The microencapsulation method selected should (41,51,52,55)

- ensure stability or biological activity of the drug;
- yield microspheres in a desired size range (microparticles of size less than 250  $\mu\text{m}$ , ideally less than 125  $\mu\text{m}$  have been determined to be suitable for depot delivery);
- be reproducible with regards to the quality and drug release profile from the microspheres;
- be scalable to support clinical development and commercialization; and
- not exhibit microsphere aggregation or adherence.

A number of proprietary technologies, based on minor variations in the basic encapsulating techniques discussed above, have been developed for preparing microspheres. A brief listing of those technologies is provided in Table 3. We will be discussing the various encapsulation techniques briefly in the following section.

#### **Solvent evaporation and solvent extraction.**

**Oil-in-water emulsion** The o/w single emulsion/solvent evaporation technique is the most favorable technique to encapsulate hydrophobic drugs with poor aqueous solubility but good solubility in water-immiscible organic solvents, such as methylene chloride and ethyl acetate. In this process, the drug and the polymer are dissolved in the organic solvent, followed by emulsification of the organic (oil) phase in water to form the o/w emulsion (Fig. 3A). The water phase generally contains an emulsifier, such as polyvinyl alcohol (PVA) and polysorbate 80 (PS 80). It is desirable that the drug has low solubility in the planned aqueous phase to enhance encapsulation efficiency and yield. The volatile solvent is generally removed by either evaporation to a gas phase (56), which involves prior dissolution into the continuous phase (57), or is extracted into the continuous phase (58,59). The rate of solvent removal from both the evaporation and extraction processes is dependent on the temperature and solubility characteristics of the solvent, polymer and dispersion medium, and in the case of extraction process, on the ratio of the emulsion volume to the quench medium volume (60). Solvent removal by the extraction process is faster than that by the evaporation process, and hence the microspheres made by the extraction process are generally more porous than the ones made by the evaporation process under similar conditions (60).

The o/w method has been used for a large number of drug candidates, such as neuroleptics (thioridazine, chlorpromazine, bromperidol), local anesthetics, diazepam, L-methadone, anticancer compounds (aclerubicin, lomustine, and paclitaxel) and steroids (36,61). It should be noted that for high drug loading formulations, precipitation of the drug

Downloaded from informahealthcare.com by McGill University on 01/15/13  
For personal use only

**Table 2** Marketed PLGA Depot Products

Product name	Active ingredient	Product owner	Partner	Drug release duration	Comments
Aitridox <sup>®</sup>	Doxycycline hyclate	Tolmar Inc	-	1 wk	PLA-based in situ gelling formulation delivered to the gum for the treatment of chronic adult periodontitis. The system consists of 450 mg of the ATR GEL <sup>®</sup> delivery system which is a bioabsorbable flowable polymeric formulation composed of 36.7% (PLA) dissolved in 63.3% N-methyl-2-pyrrolidone. Doxycycline hyclate equivalent to 42.5 mg doxycycline is mixed prior to administration. PLA-based system for guided tissue regeneration.
Atrisorb FreeFlow-D Decapeptyl SR	Doxycycline Hyclate Triptorelin acetate	Tolmar Inc Debiopharm Group	- psen (ex-United States)	- 1 3 mo	PLGA microspheres containing water-insoluble salts of triptorelin for prostate cancer. Other excipients include mannitol, carmellose sodium, and polysorbate 80.
Eligard	Leuprolide acetate	QLT Inc	Astellas Pharma Inc (Europe) Sanofi-Aventis (United States, Canada) Sosei (Japan) MediGene AG (Europe) Tecnofarma (Latin America) Luxembourg Pharmaceuticals (Israel) Han All (Korea) Tecnofarma International (Central and South America)	1 3 4 6 mo	PLGA/PLA in situ forming gel administered SC for the treatment of prostate cancer.
Lectrum depot	Leuprolide acetate	Eirochem S.A. (Latin America and Asia)	-	1 3 mo	Lyophilized PLGA/PLA-based microspheres for uterine leiomyomas, endometriosis, prostate cancer, or precocious puberty.
Leuprolide 14 day	Leuprolide acetate	Oakwood Laboratories LLC	-	2 wk	PLGA microspheres of GnRH for the treatment of prostate cancer.
Leuprorelin acetate injection	Leuprolide acetate	Dongkook Pharmaceutical Co. (Korea)	-	1 3 mo	PLGA microspheres for SC administration to treat breast and prostate cancer.
Lupride 1 month	Leuprolide acetate	Sun Pharmaceutical Industries (India)	-	1 mo	PLGA microspheres for M administration to treat prostate cancer and endometriosis.

(continued)

Downloaded from informahealthcare.com by McGill University on 01/15/13  
For personal use only

**Table 2** Marketed PLGA Depot Products (*continued*)

Product name	Active ingredient	Product owner	Partner	Drug release duration	Comments
Lupron depot	Leuprolide acetate	Takeda Pharmaceutical Co Ltd	Abbott Laboratories (United States Canada) Orion Corp (Northern Europe)	1 3 4 mo	PLGA/PLA microspheres with diluent presented in pre-filled syringe for M administration to treat endometriosis and prostate cancer. The front chamber pre-filled dual-chamber syringe contains leuprolide acetate PLGA/PLA and D-mannitol. The second chamber of diluent contains CMC sodium D-mannitol polysorbate 80 water for injection USP and glacial acetic acid USP to control pH
Lupron depot—PED	Leuprolide acetate	Abbott Laboratories nc	—	1 mo	PLGA microspheres for M administration to treat central precocious puberty
Luporelin/luposhere 1 month	Leuprolide acetate	Pepton nc	Daewoong Pharmaceutical Co Ltd (Korea)	1 mo	PLGA microspheres for SC administration for the treatment of breast cancer prostate cancer endometriosis and precocious puberty
Nutropin depot	Somatropin (growth hormone)	Genentech (Roche) nc	—	2 wk 1 mo	PLGA microspheres for SC administration to treat growth failure. Supplied in vials containing somatotropin zinc acetate zinc carbonate and PLGA. The diluent is composed of 3% CMC sodium salt 0.1% polysorbate 20 in normal saline
Risperdal Consta	Risperidone	Janssen Pharmaceutica Products LP	Janssen-Cilag N V (Europe United Kingdom) Janssen-Cilag N V (Japan)	2 wk	PLGA microspheres with 38% drug loading administered M for the treatment of schizophrenia bipolar disorder. The microspheres are reconstituted in 2 mL diluent (polysorbate 20 sodium carboxymethyl cellulose disodium hydrogen phosphate dihydrate citric acid anhydrous sodium chloride sodium hydroxide and water for injection) prior to administration
Salvacy/Moapar 3 months	Triptorelin pamoate	Debiopharm Group	European Pharmaceutical Partner	3 mo	Lyophilized PLGA microspheres for SC administration for reversible reduction of testosterone to castrate levels. The diluent consists of 8.5% mannitol USP 3% CMC sodium USP 0.2% polysorbate 80 NF

Downloaded from informahealthcare.com by McGill University on 01/15/13  
For personal use only

Sandostatin LAR	Octreotide acetate	Novartis AG	-	1 mo	PLGA microspheres administered M after reconstitution for the treatment of acromegaly
Sinofuan	Fluorouracil	Sinocere Pharmaceutical Group (China)	-	-	Sustained-release implant for multiple cancer indications
Somatuline LA	Lanreotide acetate	Teijin Pharma Ltd (Japan)		2 wk	PLGA microspheres for M administration for the treatment of Acromegaly and for the relief of symptoms associated with neuroendocrine tumors
Suprefact depot	Buserelin acetate	Sanofi-Aventis	-	2-3 mo	PLGA-based rods for SC implantation for treatment of advanced prostate cancer
Trelstar depot	Triptorelin	Debiopharm Group		1 mo (depot)	Lyophilized PLGA microspheres for M administration for treating prostate cancer
Trelstar LA	Triptorelin pamoate	Paladin Labs nc (United States)		3 mo (LA)	The diluent consists of 8.5% mannitol USP 3% CMC sodium USP 0.2% polysorbate 80 NF
Vivitrol injectable suspension	Naltrexone	Alkermes nc	Janssen Pharmaceutica Products LP (Russia)	1 mo	PLGA microspheres for reconstitution prior to M administration with Naltrexone loading of ca 33% for the treatment of alcohol abuse and opioid dependence
Zoladex implant	Goserelin acetate	AstraZeneca PLC	-	1-3 mo	Delivery diluent contains CMC sodium salt polysorbate 20 sodium chloride and water for injection Cylindrical 1mm-diameter PLGA-based implant administered SC using a 16G hypodermic needle for the treatment of advanced prostate cancer breast cancer and endometriosis

Abbreviations PLGA poly(lactide-co-glycolide) PLA poly(DL-lactide) CMC carboxymethylcellulose

**Table 3** Proprietary Encapsulation Technologies and Related Patents

Encapsulation technology	Company	Encapsulation process	Reference
PolyShell	Akina, Inc.	Solvent exchange double emulsion	WO03053325 (A3), EP1404516 (A3)
Injectable depot technology by coacervation	Alkermes, Inc.	Coacervation	US2004228833
Medisorb	Alkermes, Inc.	Solvent evaporation/extraction emulsion method	US2003113380, US6110921, US5650173
ProLease <sup>®</sup>	Alkermes, Inc.	Solvent evaporation/ extraction emulsion method	US6051259
West Pharma injectable depot technology	Archimedes Pharma	Solvent extraction emulsion method	US5869103
Microcoat	Biotek, Inc.	Solvent evaporation	US4623588
SRI/Brookwood injectable microspheres	Brookwood Pharmaceuticals (now SurModics)	Solvent extraction emulsion method	US4897268, US5407609
Depocore	CeNeS Pharmaceuticals	Coacervation	US2003180368
Debio <sup>®</sup> PLGA 2	Debio	O/W emulsion method/phase separation	US5445832
Mimplant microgranules	Debio	Solventfree extrusion process	US6319512
Extruded injectable beads	Debio	Solventfree extrusion process	US5134122
SynBioSys	InnoCore	Solvent evaporation/extraction emulsion method	WO2005068533, EP1555278
Oligosphere <sup>®</sup>	MacroMed, Inc.	Solvent evaporation/extraction emulsion method	US5100669, US5665428
ChroniJect	Oakwood Laboratories	Solvent evaporation/extraction emulsion method	US5945126
SmartDepot	Pepton	Spray drying	WO2004112752, WO2005023224
TheraPhase			
ProPhase	PR Pharmaceuticals	Solvent evaporation/extraction emulsion method	US6706289 and family
CoPhase			
CriticalMix <sup>™</sup>	Critical Pharmaceuticals	Supercritical CO <sub>2</sub> without solvents or high temperature	US6414050, US6670407

out of the polymer phase is very likely and thus, understanding the phase behavior of the drug polymer system and kinetics of precipitation, including particle size and polymorphism of the drug, become critical factors influencing drug release from the matrix.

**Solid-in-oil-in-water emulsion** The *s/o/w* emulsion technique is applicable when a specific drug is not soluble in the carrier solvent or solvent mixture, or when extensive drug loss to the continuous phase cannot be avoided when employing a cosolvent system. A lot of early research on hydrophobic drug encapsulation (such as norethisterone) as a contraceptive utilized this technique (49). Recently, the *s/o/w* technique has been used for the encapsulation of hydrophobic drugs such as levonorgestrel (62),  $\beta$ -estradiol (63), haloperidol (64), and camptothecin and its derivatives (65). Since drug particles are encapsulated directly, it is important that the particle size of the drug is small and well controlled. Generally, particle sizes of less than 10  $\mu\text{m}$ , preferably in the 1 to 2  $\mu\text{m}$  range, are desirable to improve drug loading and the uniformity of drug distribution within and amongst microspheres. Besides small particle size of the drug, careful control of drug sedimentation (in the suspension medium) or floatation (due to adhesion of bubbles to hydrophobic surfaces) during the encapsulation process must be achieved. Drug particles adsorbed on the surface of prepared microspheres (especially if the drug particle size is large) could lead to a burst release (63). This

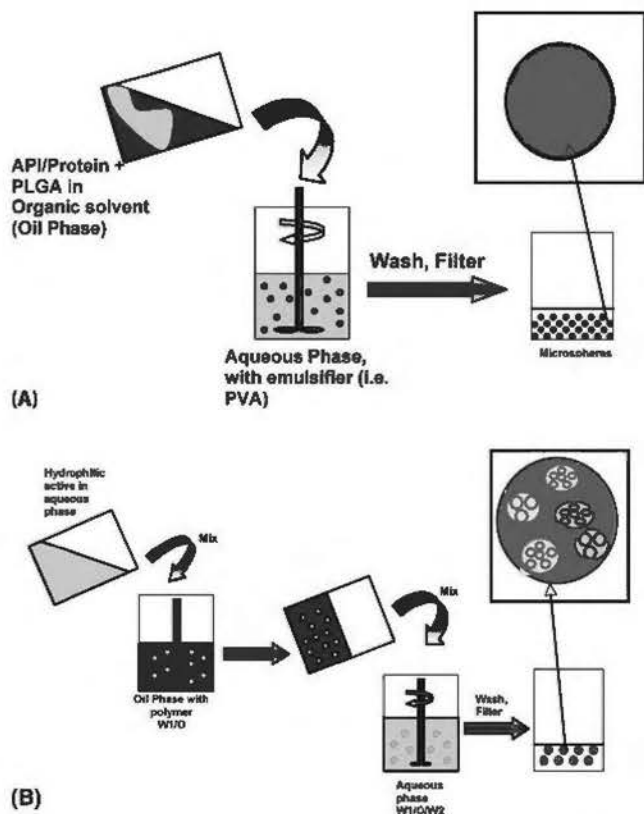


Figure 3 Schematic representations of the (A) single oil in water emulsion and (B) double water in oil in water emulsion processes for making microspheres.

Downloaded from informahealthcare.com by McGill University on 01/15/13  
For personal use only

issue could potentially be alleviated by addition of an extra polymer coating step for s/o/w microspheres, as has been suggested in the literature (66). The s/o/w microspheres tend to form large voids and channels as the drug particles dissolve, leading to better access of the dissolution medium into the microspheres, and resulting in a faster release profile as compared with monolithic microspheres prepared by the o/w emulsion technique.

**Water-in-oil-in-water emulsion** The  $w_1/o/w_2$  encapsulation method is a commonly used method for hydrophilic compounds with high aqueous solubility, such as peptides, proteins, and vaccines (40,41,53). One of the first challenges with this technique was low encapsulation efficiency of hydrophilic molecules, as described by Okada et al. (U.S. patent 4652441), which was overcome by performing  $w_1$  phase solidification. Briefly, the process comprises dissolving the active molecule in a suitable buffer, and then adding this to an organic phase (e.g., dichloromethane) containing dissolved PLGA, under controlled stirring to form the first  $w_1/o$  emulsion (Fig. 3B). This emulsion is then introduced with stirring into the second water phase, containing an emulsifier (e.g., PVA) to form the  $w_1/o/w_2$  emulsion. The organic solvent is either removed by evaporation (reduced pressure or stirring) or extraction (dilution into a large quantity of water with or without surfactant). The microspheres are then washed, separated (e.g., by filtration, sieving, or centrifugation), and then dried or lyophilized to give the final product. During the development of this technique, various formulation and process variables were evaluated to optimize drug loading, encapsulation efficiency and release profiles (67-71).

**Phase separation technique.** Unlike the o/w emulsification technique, the phase separation, or coacervation, technique is suited for both water-soluble and water-insoluble drugs. However,



the coacervation process is mainly used for hydrophilic molecules, such as peptides and proteins. The process consists of precipitating (or phase separating) the polymer from the organic solution by the addition of a nonsolvent to yield drug-containing microspheres. In brief, the drug is either dissolved in water and then added to the polymer-containing organic phase (o/w emulsion), or directly added to form a solution in the organic phase. To this, an organic nonsolvent is added with stirring, which extracts the polymer solvent. This leads to phase separation of the polymer to form coacervate droplets, which entrap the drug. The microspheres thus formed are hardened by transferring to a larger quantity of organic nonsolvent, washed, filtered, sieved and dried (54,72). The various factors that influence the final product include addition rate of the first nonsolvent, concentration of the polymer, stirring rate, temperature, or addition of an additive (to alleviate stickiness of the coacervate droplets). Since the process does not utilize addition of an emulsion stabilizer, agglomeration might become a frequent problem.

**Melting and spray-drying techniques.** Melting and spray drying have been utilized to prepare microspheres in cases where conventional processing methods, such as o/w and w/o/w emulsion, do not provide the required throughput and product stability. Spray drying is rapid, convenient, easy to scale-up, utilizes mild conditions, and is less dependent on the solubility parameter of the drug and the polymer (41,73,74). Compared with the conventional emulsion methods, the spray drying method requires larger batch sizes (limitation if small amounts of bulk available), results in larger losses due to adhesion of microparticles to the apparatus, and is reported to cause agglomeration of the microparticles (74). Modifications to the spray drying technique have been incorporated, such as a double nozzle technique to reduce agglomeration. Spray dried formulations for a range of compounds, such as theophylline, progesterone, and piroxicam, have been reviewed in the literature (36).

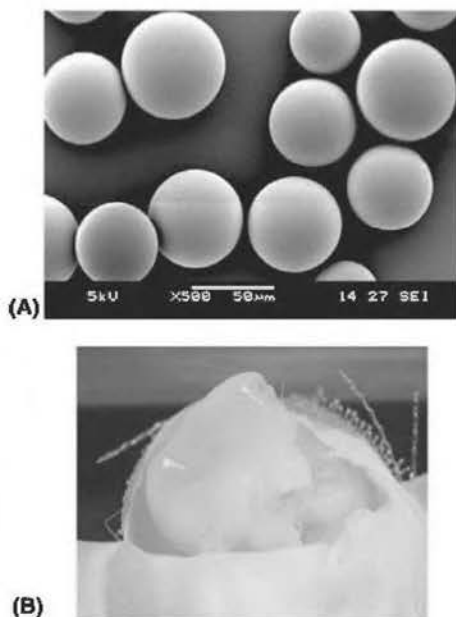
Melting is a technique that avoids the use of organic solvents, but requires the dispersion or melting of the drug in a polymer melt. To generate microspheres from this hot melt, a water-soluble polymer that is not miscible with the drug/polymer melt can be employed. The resulting emulsion can be solidified by cooling, and the microspheres can be collected by dissolving the water-soluble polymer matrix in a large volume of water (European Patent EP 934 353). An alternative method is to grind/jet-mill the drug/polymer matrix after cooling (33,61,75). The improvements in this technology have focused on generating more uniform particles by introducing an extrusion step in the process, and getting spherical and smaller particles by emulsification in a hot solution containing an emulsifier (61). Microspheres produced by the melt technique generally lead to nonporous polymer matrices, which subsequently lead to slower release rates from the depot, especially for hydrophobic drugs.

#### *PLGA Gel/Rod Systems*

Although microspheres (Fig. 4A) have been predominant, other PLGA-based depot systems have also been developed, including in situ forming gels, and rods for implantation. In this section we will discuss some of the PLGA-based gel and rod systems briefly, and highlight the advantages and disadvantages of such systems.

The in situ gelling systems are presented as liquids or semi-solids with a wide range of viscosity, containing a biodegradable polymer and drug dispersed or dissolved in the liquid phase of the delivery system (solvent/cosolvent system). Upon SC or IM administration, a depot is formed at the site of injection (Fig. 4B). Such systems are usually manufactured through aseptic processing, however,  $\gamma$ -irradiation for terminal sterilization of the product has been evaluated as well. The in situ forming depots have been classified into different categories, depending on the depot-forming mechanism (76,77).

The in situ precipitating system consists of PLGA dissolved in a water-immiscible or partially miscible organic solvent, which also dissolves/disperses the drug to form a solution/suspension. Once administered, the organic solvent escapes, allowing water ingress and precipitation or phase separation of the drug/polymer system, leading to the formation of a depot. Depending on the solubility of the drug in the organic phase, these systems are generally associated with high initial burst. The initial burst is also dependent on the



**Figure 4** (A) Scanning electron micrograph of PLGA microspheres and (B) photograph of an in situ forming PLGA gel depot explanted from a rat. *Abbreviation:* PLGA, poly(lactide co glycolide).

hydrophobicity and concentration of PLGA, water miscibility of the organic solvent, and the aqueous solubility and loading of the drug. Subsequent drug release from the depot is dependent on the degradation/erosion of PLGA. Eligard<sup>®</sup>, which uses the Atrigel<sup>®</sup> technology from QLT, (78) has received regulatory approval. The Atrigel<sup>®</sup> technology involves the dissolution of polymer and drug in *N*-methyl-2-pyrrolidone, but has also utilized other organic solvents such as propylene glycol, dimethyl sulfoxide, tetrahydrofuran, triacetin and ethyl benzoate to control initial burst. The biocompatibility and systemic toxicity of these organic solvents, when administered intramuscularly or subcutaneously, have been of concern. Alzamer<sup>®</sup> technology, developed by Alza, also utilizes PLGA as a carrier for in situ depot formation, however, this technology utilizes more lipophilic solvents, such as benzyl alcohol, to reduce irritation and initial drug burst.

Thermally induced gelling systems are exemplified by the water-soluble ReGel<sup>®</sup> triblock copolymer, composed of the hydrophobic PLGA (A) and hydrophilic PEG (B) blocks in the ABA configuration, which is a solution under ambient conditions, but turns into a gel at body temperature. OncoGel<sup>®</sup> is a six-week sustained-release depot of paclitaxel that utilizes this system. The release from the ReGel polymer system is controlled by controlling the hydrophilicity/hydrophobicity, molecular weight, concentration and polydispersity of the copolymer (79).

Implantable PLGA-based biodegradable systems have also been explored. Zoladex<sup>®</sup> is a one- and three-month PLGA depot of goserelin acetate for the treatment of prostate cancer. Durect is developing the PLGA-based Durin<sup>®</sup> implant, containing Leuprolide for Alzheimer's disease. Durin is a reservoir-type implant where the drug release is controlled by the drug loading, polymer molecular weight and composition, geometry of the device, and permeability of the membrane (WO03000156 from Southern Biosystems Inc).

#### *Delivery of Proteins and Peptides*

Peptides and proteins have become a vital class of therapeutics, however, many issues exist in the delivery of biologically active macromolecules to target tissues. Upon injection, peptides and proteins are rapidly cleared because of proteolytic degradation, efficient renal clearance, neutralization by antibodies, and rapid distribution to tissues outside the blood stream. The

rapid clearance results in the need to dose peptides and proteins on a very frequent basis, which is a painful and inconvenient dosing regimen and often results in poor patient compliance. Several strategies have evolved to overcome the challenge of short half-life, including increasing the molecular size of the protein via conjugation of high molecular weight biopolymers (80) and site-directed mutagenesis to remove proteolytic cleavage sites. Over the last 25 years, much pharmaceutical research has gone into developing improved delivery systems aimed at delivering real patient value by providing another means of overcoming these challenges. Formulation strategies include injection of crystalline or amorphous peptide or protein particles (81), implantable osmotic pump devices, and sustained-release polymeric depot systems.

The development of peptide and protein depot systems can involve significant challenges beyond those typically encountered with small molecules. Polypeptides are inherently unstable because of their physicochemical and biochemical properties, which stem in part from their large molecular size. Quite simply, more can go wrong with larger molecules. Proteins have secondary, tertiary and often quaternary structure that all contribute to the three dimensional orientation necessary for proper protein function. The processes outlined earlier for manufacturing depot systems, which can include high-shear mixing, pumping, organic solvent/aqueous interfaces, surfactants, contact with hydrophobic surfaces, sudden pressure differentials, heat, and drying, are all detrimental to the delicate structure of a protein. The more successful formulation strategies have sought to minimize protein unfolding and aggregation by reducing process stress and carefully considering the additives/solvents used. Additives and solvents can cause protein denaturation by perturbing their physicochemical stability, and the use of solvents is therefore an important consideration for polypeptide depot development (82). In addition to their inherent physicochemical instability, proteins are also sensitive to chemical degradation (83). In particular, asparagine deamidation and hydrolytic cleavage are accelerated as a result of the acidic environment created when PLGA breaks down via ester bond hydrolysis (84,85).

Despite the aforementioned challenges, several peptides are commercially available as sustained-release depots, including leuprolide, triptorelin, histrelin, goserelin and octreotide. Images include biodegradable microspheres and rods, as well as nonbiodegradable polymer rods and titanium-based implantable osmotic pump devices. Once-monthly Lupron Depot<sup>®</sup> (Leuprorelin acetate suspension for SC injection) was the first sustained-release peptide approved in the United States, in 1989 (38). Since this approval, longer-acting images have been produced and today three-, four-, and six-month and one-year delivery options are available.

The only protein depot to receive FDA approval was Nutropin Depot<sup>™</sup>. Nutropin Depot<sup>™</sup>, approved in 1999 as a treatment for growth hormone deficiency in pediatric patients, is a sustained-release form of Genentech's human growth hormone [somatropin (rDNA origin)] using Alkermes' PLGA-based ProLease<sup>®</sup> technology. The once or twice-monthly injection (based on the patient weight) offered an alternative to multiple weekly injections. Unfortunately, the product had a short lifetime and was pulled from the market in June of 2004, citing the high cost of production and commercialization. Although the drug was discontinued, the successful development and approval of this complex dosage form signified major success for those working on sustained-release dosage forms for biologics. There was a large leap in complexity in producing Nutropin Depot<sup>™</sup> compared with the smaller octa-, nona- and decapeptides mentioned previously. These peptides do not possess the secondary structure of most proteins (alpha-helix or beta-sheet) and are quite stable, having properties more like small molecules. In contrast, human growth hormone contains 191 amino acids and both secondary and tertiary structure.

The Nutropin Depot<sup>™</sup> approval took years of commitment and was the result of a well-designed manufacturing strategy, which focused specifically on stabilizing the protein structure (86-88). The manufacturing process, based on the work of Gombotz (89), was different from other, more conventional s/o/w microsphere manufacturing processes, as it utilized low temperature processing, excipient-based protein stabilization, and release-controlling agents. On the basis of this work, and the work of many others, many of the technical challenges inherent to developing PLGA-based sustained-release biologics have been defined, opening the way for rational design of molecules (especially peptides) for sustained-release delivery. Synthetic peptides can be designed and/or screened to be less sensitive to the low pH environment of a degrading microsphere. Reactive amino acids like lysine, with its

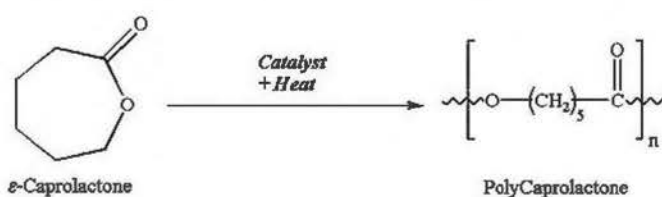
nucleophilic primary nitrogen, can be removed or capped to avoid amide formation that can result in covalent peptide-PLGA conjugates. If the desire is a PLGA-based protein delivery system, early forced degradation screening utilizing conditions which mimic PLGA degradation, as well as a screen of manufacturing stress conditions, should be conducted to select the protein with the highest stability. Having very early insight into the desired final product image will better allow for the rational design of the proper characteristics, which will, in turn, ensure manufacturability later in development.

### Other Degradable Depot Delivery Systems

#### Natural and Synthetic Polymers

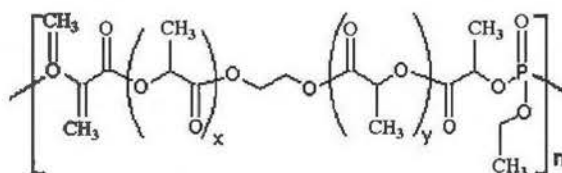
A number of natural and synthetic biodegradable polymers have been investigated for depot delivery, although only few of them have demonstrated biocompatibility. Natural biodegradable carriers like bovine serum albumin (BSA), human serum albumin (HSA), collagen, gelatin, and hemoglobin have been studied for drug delivery (41), but their use is limited by their high costs and questions over purity. Thus, in the last two decades, synthetic biodegradable polymers have been widely used. In this section we will summarize such biodegradable depot systems and highlight the various depot delivery technologies utilizing those polymers.

**Polycaprolactones.** Poly- $\epsilon$ -caprolactone (PCL) is a biodegradable polyester with a melting point around 60°C and a glass transition temperature of approximately 60°C (90). It is semicrystalline and is known to degrade slower than polylactide under physiological conditions and thus, is suitable for release extending to a period of greater than one year. A variety of drugs including antigens, antihypertensives, chemotherapeutic agents, and antibiotics have been evaluated with regards to encapsulation in PCL microspheres (91).



PCL can be an attractive polymer for encapsulating proteins since the degradation of PCL will not result in an acidic environment that is detrimental to protein stability (9). This has been exemplified with PCL microspheres of insulin (92). Block copolymers of caprolactone with PLA, PLGA, PEG, or PEO have also been evaluated for drug delivery (93-95). Capronor is a biodegradable polymer system for the sustained subdermal delivery of contraceptive steroids. Capronor utilizes PCL as the polymer and was evaluated in phase II clinical trials as a contraceptive however, the product did not make it to market.

**Polyphosphoesters.** Polyphosphoesters (PPE) are a group of structurally versatile biodegradable polymers (degrade via hydrolysis and possibly enzymatic digestion at the phosphoester linkages) that have found application in drug delivery because of their biocompatibility and similarity to bio-macromolecules such as nucleic acids (96).



PPE has been used as a carrier for sustained delivery of low molecular weight drugs (97), proteins (98), and DNA (99). Guilford Pharmaceuticals (now MGI Pharma) had a product

candidate, Paclimer<sup>®</sup>, a poly (lactide-co-ethylphosphate) microsphere formulation of paclitaxel, designed to deliver paclitaxel over eight weeks for the treatment of ovarian cancer.

**Polyanhydrides.** Polyanhydrides (PA), as the name suggests, are biodegradable copolymers with a hydrophobic backbone of anhydride linkages formed by the condensation reaction of two fatty acids. Their applications in parenteral drug delivery have been reviewed for a variety of therapeutic agents such as growth hormone, anticancer agents, antibiotics, local anesthetics, anticoagulants, anti-inflammatory, and neuroactive drugs (100,101). Polyanhydride microspheres can be prepared by spray drying, hot-melt encapsulation or emulsion methods. Because of release mediated by surface erosion, they are believed to better protect unreleased drug from the release medium (9,101). Various types of homo- and hetero-PAs consisting of aliphatic, aromatic, heterocyclic and other monomers have been studied in detail and extensive work on PA carriers resulted in clinically used implants like Gliadel<sup>®</sup> (MGI Pharma, Inc.) and Septacin<sup>™</sup> (Abbott Laboratories). Gliadel is a polyanhydride polymer matrix of poly[bis(p-carboxyphenoxy) propane] with sebacic acid P(CPP:SA) (20:80 molar ratio) containing BCNU for the treatment of brain tumor. BCNU is a nitrosourea with short half-life but is considered a "gold standard" for treating glioblastomas. Gliadel wafer is a sterile, off-white to pale yellow wafer with a diameter of 1.45 cm and 1 mm thickness. Each wafer contains 7.7 mg BCNU and 192.3 mg PA copolymer. Septacin<sup>™</sup> is a PA implant consisting of P(FAD:SA) (1:1 weight ratio) polymer and gentamicin for the treatment of osteomyelitis. Each implant has five beads in a strand with each bead being 12 mm long and 4 mm in diameter weighing 150 mg (contains 20 mg gentamicin as gentamicin sulfate) (102).

**Polyortho esters.** Polyortho esters (POE) are generally synthesized by condensation of diols and a diketene acetal, and often involve copolymerization with a latent acid such as glycolic acid and lactic acid (a class of POE called Biochronomer<sup>®</sup>, which have been developed by AP Pharma) to allow control over the hydrolytic degradation of the ortho ester linkages (9,103). POEs are thermoplastic polymers that have been demonstrated to be stable to 24 kGy  $\gamma$ -irradiation and can be easily formulated as microspheres using extrusion followed by cryogenic milling (104,105). Various processes have been employed to prepare POE microspheres including spray congealing (106), emulsion-solvent evaporation (low encapsulation efficiency with water-soluble drugs) (107,108), and extrusion of block copolymers of PEG and POE to enhance encapsulation efficiency with water-soluble compounds (109).

**Block copolymers of polybutylene terephthalate.** Multiblock copolymers of hydrophilic PEG and hydrophobic polybutylene terephthalate (PBT), known as PolyActive<sup>™</sup>, have been developed by OctoPlus. The degradation of these biodegradable and biocompatible polyether ester copolymers occurs by hydrolysis of the ester bonds and oxidation of the ether linkages (110,111). OctoPlus is currently developing Locteron<sup>™</sup>, a microsphere formulation of interferon  $\alpha$ , using this technology.

**Cross-linked dextran.** Cross-linked dextran is a biodegradable and biocompatible (112,113) hydrogel system for drug delivery, specifically protein delivery, which has been developed by OctoPlus. A modified dextran derivatized with hydroxyethyl methacrylate (dex-HEMA), referred to as OctoDEX<sup>®</sup>, has been reported to be able to tailor the release of proteins from microspheres from days to months (114-116).

**Polyamino acid polymers.** Polyamino acid polymers, as the name suggests, are composed of naturally occurring amino acids. The release duration can be tailored, in principle, by modifying the hydrophobicity of the participating amino acids in the block copolymer. Flamel Technologies has developed these polymer systems for protein delivery. An amphiphilic block copolymer, composed of L-leucine and L-glutamate, is referred to as Medusa I<sup>®</sup> (117). These are self-assembling systems, which are noncovalently associated with proteins. Insulin (Basulin<sup>®</sup>) is one of the proteins that is being investigated with this technology for type I diabetes, with a target release duration of two days. Flamel has also developed Medusa II<sup>®</sup>,

which is hydrophobically modified L-glutamate, for release over two weeks. Interferon  $\alpha 2b$  and Interleukin-2 are also being developed using this technology (118).

**Cellulosic polymers.** Water-soluble anionic polymers, such as CMC, have been utilized to form water-insoluble complexes with soluble cationic peptides. Such insoluble complexes, formed by ionic interactions, have been developed (Rel-Ease<sup>®</sup>) for sustained drug delivery by Praecis. Plenaxis<sup>®</sup> is an abarelix-CMC complex that utilized Rel-Ease<sup>®</sup> technology and was approved in 2003 for the treatment of advanced prostate cancer; however, it was withdrawn in 2005 because of financial considerations (119-121).

**Cross-linked albumin.** Use of cross-linked albumin for sustained-release applications is exemplified by the ProMaxx<sup>®</sup> drug delivery technology, which was developed by Epic Therapeutics, Inc, a wholly-owned subsidiary of Baxter Healthcare Corporation. ProMaxx is a protein matrix-based technology developed for protein, peptide, and small molecule delivery. The microspheres, in the particle size range of 0.5 to 40  $\mu\text{m}$ , are produced in an aqueous medium by mixing a carrier protein (e.g., HSA), a water-soluble polymer (e.g., hetastarch), a polyanionic polysaccharide (e.g., dextran sulfate, heparan sulfate, and polyglutamic or polyaspartic acid), and a divalent metal cation (e.g.,  $\text{Ca}^{2+}$  and  $\text{Mg}^{2+}$ ). The release from the microspheres can be controlled by varying the concentration of hetastarch, temperature, pH, albumin, or length of heat exposure of microspheres. Baxter is developing LeuProMaxx<sup>®</sup> (one- and three-month release of leuprolide acetate) using the ProMaxx technology, for the treatment of prostate cancer (9,122).

**Other gel-forming polymer systems.** The SABER<sup>®</sup> system, from Durect Corporation, consists of a hydrophobic polysaccharide, sucrose acetate isobutyrate (SAIB), as the drug release-controlling matrix. SAIB, along with the drug, is dissolved/dispersed in ethanol, benzyl alcohol, or other water-miscible solvents. Since this system has a relatively low viscosity, administration with a smaller gauge needle is easier compared with PLGA-based gel systems. Sustained-release formulations of bupivacaine (123) and rhGH (124) are being considered for feasibility assessment or development.

A cross-linked PEG-based copolymer (containing multiple thio (-SH) groups along the polymer backbone) which forms a hydrogel when mixed with  $\alpha$ , omega-divinylsulfone-PEG (2 kDa) dissolved in a neutral phosphate buffer has been reported (125). The system has been proposed to achieve a release over two to four weeks, with application mostly suited toward large molecules. Mild adverse tissue reactions have been reported in biocompatibility studies in rabbits and rats.

GelSite<sup>®</sup> polymer, from DelSite biotechnologies, is a natural acidic polysaccharide extracted and purified from the aloe plant. The polymer forms a gel in the presence of calcium (in situ cross-linking) when injected subcutaneously or intramuscularly, and thus entraps a water-soluble drug (e.g., a protein) providing sustained release (U.S. patent 5929051). The polymer has also been shown to specifically bind to, and stabilize, heparin binding proteins, thus providing additional control over drug release without affecting the biological function (U.S. patent 6313103).

Chitosan is a pH-dependent cationic polymer (amino polysaccharide) that has been demonstrated to be biocompatible and biodegradable. Chitosan can form an in situ thermosensitive gelling system when combined with an anionic polyphosphate salt, glycerophosphate (GP) (126,127). A chitosan-GP gelling system has been evaluated for camptothecin delivery, providing zero-order release over four weeks (128).

Poloxamer<sup>®</sup> 407 is a triblock copolymer of polyoxyethylene and polyoxypropylene units in the ABA configuration. Mostly utilized as a nonionic surfactant, this water-soluble polymer demonstrates reverse gelling properties. A 20% or higher polymer solution is a liquid at low temperatures, but gels at body temperature (129). Although this approach potentially provides an exciting system for sustained release of large molecules, because of the lack of organic solvents, its application has been limited by a lack of biodegradability, cytotoxicity concerns, and reports of increased levels of plasma cholesterol in rats administered with poloxamer intraperitoneally (130).

### *Lipid Based Systems*

Conventional lipid-based depot systems, such as oil solutions or suspensions, have been discussed earlier in this chapter. Conventional lipid systems rely on the partition of drug from the oil phase into the aqueous phase at the injection site to control release. Advanced lipid-based dispersed systems, with particles in the submicron size range, have been developed for water-soluble and water-insoluble drugs for parenteral administration. Natural and synthetic phospholipids, with or without further chemical modifications, have not only been used in stabilizing triglyceride-based lipid formulations, but also are the major structural components of lipid vesicles. Though lipid-based systems including emulsions provide an opportunity for sustained release, the duration of release is seldom over one week. In this section we will briefly discuss a few such lipid-based systems.

**Liposomes.** Liposomes are vesicles composed of an inner aqueous core surrounded by a phospholipid bilayer. Liposomes are primarily categorized into three types multilamellar vesicles (MLV), small unilamellar vesicles (SUV) and large unilamellar vesicles (LUV). Optimization of the bilayer composition, charge, and size of liposomes, as well as the internal aqueous composition, allows efficient incorporation of a wide variety of drugs (131). Liposomes, with or without surface pegylation, have been evaluated extensively for various compounds for intravenous administration (9). Doxil<sup>®</sup> (doxorubicin HCl) liposome injection from Alza Corporation was the first pegylated liposomal doxorubicin product approved for the treatment of refractory ovarian cancer and AIDS-related Kaposi's sarcoma. However, as a depot delivery system for SC and IM use, liposomes have not proven to be the best candidates despite being biocompatible and demonstrating positive results for efficacy (132). The primary reason for this lack of success is the relatively limited drug-loading capacity and short duration of release for the entrapped drugs. This is coupled with a complex manufacturing process, and physical stability considerations (9).

**Multivesicular liposomes.** SkyePharma developed the DepoFoam<sup>™</sup> [now owned by Pacira Pharmaceuticals, Inc. (133)] technology, which consists of tiny, lipid-based particles, 10 to 30  $\mu\text{m}$  in size, composed of hundreds to thousands of discrete water-filled chambers containing the encapsulated drug, with each chamber separated from adjacent chambers by a bilayer lipid membrane. The bilayer is composed of synthetic phospholipids (dioleoyl phosphatidylcholine and dipalmitoyl phosphatidylglycerol), cholesterol and triglyceride (134). Drug release from DepoFoam particles is achieved by diffusion through the walls, gradual erosion of the particles, and by processes involving the rearrangement of membranes. DepoCyt<sup>®</sup> is the first approved DepoFoam product containing cytarabine for the treatment of lymphomatous meningitis, administered intrathecally every two weeks. DepoDur<sup>®</sup> is a morphine sulfate formulation for postsurgical pain relief, given epidurally every two days. DepoBupivacaine<sup>®</sup>, a sustained-release formulation of bupivacaine, is in phase III development for local anaesthesia/pain. Proteins and peptides have also been evaluated with the DepoFoam technology with regards to in vitro and in vivo release (135).

**Lipid microparticles.** Lipid microparticles are solid lipid-based drug delivery systems composed of a dissolved or dispersed drug in a solid lipid matrix. The low mobility of the drug in the lipid matrix and hydrophobic nature of the lipids provide the required sustained-release properties (136). A maximum loading capacity of 25% has been reported for these systems (137). Various methods of encapsulation have been utilized to produce these microparticles, such as solvent-evaporation, melt-dispersion or spray-congealing methods (138). Lipid microparticles have been evaluated for the sustained release of small molecules such as local anesthetics and antibiotics, as well as proteins and peptides (139-142).

**Cochleates.** Cochleates are formed by the condensation of small, unilamellar, negatively charged liposomes composed of an anionic phospholipid, such as phosphatidylserine. The small liposomes fuse to form larger lipid bilayer sheets in the presence of a cation, such as calcium. These sheets roll up into cinnamon stick-like or cigar-like structures to minimize the interactions between water and the hydrophobic surface of the sheet. The cochleates are

characterized by a tightly-packed bilayer with little or no internal aqueous phase (143). Depending on the hydrophobicity and charge of the molecule, it could either be embedded in the bilayer, or encapsulated between the bilayers (144). The characteristics of cochleates lend themselves to application via the intravenous route to increase drug circulation time (e.g., amphotericin B cochleates), and ability to penetrate and accumulate in target tissue (145,146). Recently, delivery system for vaccines (147,148) and genes (149), have utilized cochleates as well.

#### **IMPLANTABLE DEVICE-BASED AND NONDEGRADABLE DEPOT DELIVERY SYSTEMS**

One of the key aspects of an implantable, nondegradable depot delivery system is the requirement for a minor surgery for implantation, and a similar procedure for explanation of the implant once the dose has been delivered. Hence, a longer duration of drug release is required to maintain patient acceptability. Although the administration involves an invasive procedure, in the case of adverse effects, removal is straightforward. Generally, implants would not be considered where the drug dose is dependent on body weight, since the dose and release from these systems is predetermined. However, in cases where a broad therapeutic window exists and sustained drug levels are required, implants present themselves as a viable option. In this section we will briefly discuss some of the nonbiodegradable implants including polymeric systems, osmotically driven systems and other device-based systems.

##### **Polymeric Systems**

The nondegradable polymers can be processed with drug to yield depot systems of various configurations, which can then be implanted subcutaneously. Two primary categories for nondegradable polymeric systems are the encapsulated reservoir system and the matrix-loaded system. One of the leading examples of the encapsulated reservoir system is the Norplant<sup>®</sup> implant from Wyeth. Norplant is a five-year levonorgestrel implant for contraception, approved by the FDA for use in women. The implant, which consists of six flexible closed capsules, is a reservoir system with each capsule consisting of 36 mg of active in silicone rubber tubing (silastic) of 2.4 mm diameter and 34 mm length (150). Wyeth has an analogous product in the form of Jadelle<sup>®</sup>, which was designed to require fewer capsules (two) for implantation, and thus improve insertion and removal. Jadelle has been approved in the United States, but is not marketed. On the basis of the publically available prescriber's information, Jadelle is a set of two flexible cylindrical implants, consisting of a dimethylsiloxane/methylvinylsiloxane copolymer core enclosed in thin-walled silicone tubing. Each implant contains 75 mg of the progestin levonorgestrel. The implants are sealed with polydimethylsiloxane adhesive and sterilized. Each implant is approximately 2.5 mm in diameter and 43 mm in length. The implants are inserted in a superficial plane beneath the skin of the upper arm. The calculated mean daily in vivo release rate of levonorgestrel provided by the implants is about 100 µg/day at month one, followed by a decline to about 40 µg/day at 12 months, and to about 30 µg/day at 24 months, with stabilization thereafter at about 30 µg/day. One of the major drawbacks with the reservoir system is the risk of "drug dumping" if there is a rupture of the releasing membrane.

Implanon<sup>®</sup>, from Organon (now part of Merck, Sharp & Dohme Corp), is a leading example of the matrix-loaded system. Implanon is an etonogestrel implant with each implant containing 67 mg of the active embedded in an EVA (ethyl vinyl acetate) matrix, which is then surrounded by a rate-controlling EVA membrane to form a rod measuring 40 mm in length and 2 mm in diameter (150). The implant is designed to release over three years and was approved by the FDA in 2004. One of the major drawbacks with the matrix-loaded systems is a more complex release mechanism (likely diffusion controlled) which presents a significant barrier toward achieving a zero order release profile. The Hydron<sup>®</sup> implant, from Valera Pharmaceuticals (acquired by Indevus Pharmaceuticals in 2006), is a hydrogel reservoir drug delivery system designed for delivery of drugs at a predetermined rate over a one-year period. The hydrogel nature of the implant is likely to cause less discomfort when compared with metal implants. The cylindrical implant is 26 mm long, 3.5 mm in diameter and 0.5 mm in wall thickness, and is composed of a cross-linked copolymer of hydroxypropyl methacrylate and 2-hydroxyl methacrylate. The core of the implant consists of the drug (e.g., 50 mg histrelin) and



stearic acid (as in Vantas<sup>®</sup>, which is a one-year histrelin implant) (151). The implant is packaged in a glass vial containing 1.8% sodium chloride solution, which allows hydration and priming of the implant prior to insertion.

### Osmotically Driven Systems

As the name suggests, these systems utilize osmotic pressure for long-term delivery of potent therapeutic agents. The Duros<sup>®</sup> implant, from DURECT, is one such example, which consists of an outer titanium cylinder, an osmotic engine (containing sodium chloride), a piston and a drug chamber. One end of the outer cylinder is capped with a semi-permeable membrane (controls the rate), and the other end has an orifice, which releases the drug using a diffusion moderator. The implant holds a maximum of 200  $\mu$ L of the drug solution, and can be up to 4 mm in diameter and 44 mm in length. A brief description of the steps involved in the functioning of the Duros systems will include (1) water influx into the osmotic engine, (2) expansion of osmotic engine, (3) displacement of the piston, and (4) contraction of drug formulation-containing chamber to release the drug through the exit port (152). Because of the volume constraints, the implant usage is limited to potent compounds with high formulation concentrations. Solution formulations with various aqueous and nonaqueous solvents, and suspensions with nonaqueous solvents, have been evaluated with the Duros implants. Viadur<sup>®</sup>, from Alza Corporation, is a one-year leuprolide acetate implant, which received FDA approval for prostate cancer (153). DURECT is also developing Chronogesic<sup>®</sup>, a three-month sufentanil implant, for which the clinical trials are currently suspended to improve the device to mitigate performance issues.

### Other Device-Based Systems

Besides the polymeric implants and the osmotically driven systems, there are other devices, which have been utilized for the delivery of highly potent drugs. SynchroMed pump from Medtronic and Codman 3000 from Codman and Shurtleff are representative systems. The SynchroMed pump is an implantable, programmable, battery-powered device that stores and delivers medication according to instructions received from the programmer. The various models of the pump vary in size of the reservoir and the presence of a side catheter access port. The hold volume in the refillable pump can range from 10 to 40 mL. The CODMAN 3000 implantable drug delivery system features an inexhaustible power supply obviating the need for battery and provides continuous delivery with the refillable volume ranging from 16 to 50 mL. The Codman 3000 implantable pump is divided into inner and outer chambers by accordion-like bellows. The inner chamber contains the drug to be infused while the outer chamber contains propellant permanently sealed. The patient's own body temperature warms the propellant, which exerts a constant pressure on the bellows. This causes the drug to flow out of the inner chamber through a filter and flow restrictor then slowly out of the catheter.

Both these pumps require surgical insertion and removal, and the refill of these pumps will require expertise. One of the most common applications of device-based systems is for the administration of insulin. Such insulin pumps typically consist of the pump, the disposable drug reservoir, and an infusion set, which includes a canula for SC insertion. The pumps come in various models that include Ping (Animas), Cozmo<sup>®</sup> (Deltec), Spirit<sup>®</sup> (Disetronic), Paradigm 522/722 (MiniMed), OmniPod (Insulet) and Diabecare IIS (Sooil). The insulin pumps range in hold volume from a couple of milliliters, to as much as 90 mL, and are intended to deliver rapid- or short-acting insulin 24 hours a day through a catheter placed under the skin.

### DEVELOPMENT CONSIDERATIONS FOR DEPOT DELIVERY SYSTEMS

Sustained-release parenteral formulations are generally complex dosage forms, and therefore often present significant challenges during development and scaleup. These challenges include sensitivity to changing API and excipient properties, maintaining critical formulation attributes during manufacturing process development and scaleup, ensuring sterility, evaluating drug release and establishing in vitro in vivo correlations (IVIVC), setting specifications, ensuring product quality, and managing material and manufacturing costs. Regulations, standards, and science-based guidance are generally lacking for parenteral sustained-release dosage forms (154,155), and development timelines can be long. For these

reasons, it can be advantageous to initiate development of these dosage forms early in the product lifecycle.

#### **In Vitro and In Vivo Release from Depot Delivery Systems**

Selection of in vitro release methods remains a significant challenge in the development of depot formulations, and little in the way of science-based guidance for industry exists (156). Suitable in vitro release methods can reduce the dependence on in vivo testing and speed development timelines. Key uses for in vitro release methods include assessment of drug release (including burst release) during early formulation and process development and subsequent optimization, quality control to support batch release and stability evaluation, and definition of critical product attributes and critical process parameters (154-156). In vitro release methods should be biorelevant to enable a robust IVIVC for predicting in vivo release on the basis of in vitro evaluation; validated IVIVC could potentially support formulation bridging during development. For depot formulations that are designed to release over long periods of time (e.g., months), it is often not practical to rely on real-time in vitro release evaluations, and therefore accelerated methods are required (157).

#### *In Vitro Method Development*

In vitro release methods for parenteral depot formulations have been well-reviewed (157-159). Considerations for method development include the apparatus type and design, the release media, and rational selection of experimental variables such as temperature and agitation rate. Generally, three methods are used for evaluating in vitro release from parenteral depot formulations: separation methods, flow-through cells (open system), and dialysis techniques (156-160). Each has certain advantages and limitations. There are currently no regulatory standards for in vitro release testing of parenteral depot formulations, and available compendial apparatus were not designed for this purpose and are generally not suitable, with the exception of USP IV (156). Of the available methods, the separation technique is the simplest and appears to be the most widely utilized. A quantity of the dosage form is placed in a vessel, along with a specified volume of release medium, and agitated at a controlled rate and temperature. At specified timepoints, the release medium is sampled and assayed for drug content, and fresh medium is returned to the vessel. Dispersed systems must first be separated by centrifugation or filtration prior to sampling, and aggregation of dispersed systems is a concern (156). The flow-through method allows for maintenance of sink conditions, but is more complex and potentially less robust (156). The dialysis technique may provide the best approximation of the confined environment at the injection site, coupled with sink conditions in the bulk release medium, but membrane stability and drug adsorption must be evaluated (156,160).

Selection of biorelevant release media is another important aspect of method development. Many reports specify phosphate buffered saline (PBS) at 37°C as the release medium to approximate in vivo conditions, although in some cases media with different pH, ionic strength, or protein content are more appropriate. Media volume is a critical variable, particularly for drugs with solubility limitations where sink conditions may not be achieved. Media should be selected on a case-by-case basis based on the properties of the active and the formulation. Other physiological variables to consider during selection of release media and development of the method include metabolism, tissue pH and buffer capacity, vascularity, level of exercise, and volume and osmolarity of the product (156).

#### *Accelerated In Vitro Release Methods*

Accelerated methods that can promote rapid release of the depot contents over a short (e.g., few days) time period are needed for quality control (e.g., product release) and formulation development applications, particularly for very long-acting formulations (157). These methods should be capable of discriminating formulation changes that can impact bioavailability, and detecting batch to batch variability and the impact of product instability over time (155). Acceleration of release is most commonly accomplished by raising temperature (e.g., to 50-60°C), altering pH, or adding surfactants (156,157). It is important to consider the impact of

factors such as polymer transition and degradation temperatures on the release mechanism (154). To accurately assess burst release, a real-time release evaluation may be conducted in parallel to the accelerated method (154).

#### *In Vitro In Vivo Correlation*

The need to establish IVIVC for parenteral depot formulations is well recognized (154). This has historically been difficult to achieve, presumably because of the large number of parameters influencing release from depot formulations both in vivo and in vitro, including fluid volume, viscosity, tissue barriers (e.g., fibrous encapsulation), phagocytosis, and inflammation (161-163). There are, however, increasing numbers of successful reports in the literature establishing IVIVC for parenteral depot systems, and these have been recently reviewed (156,164,165). IVIVC becomes more likely as drug release from the depot is the rate-limiting step for absorption, and as release is governed primarily by diffusion, rather than polymer degradation, which can differ in vivo and in vitro (165). Steps to establish IVIVC are similar to those for oral dosage forms, and include in vitro method development, preparation of formulation variants that are expected to have different behavior in vivo, in vitro and in vivo testing, and modification/optimization of the in vitro release method to mimic in vivo results (156). Animal models, such as the rat, are suitable for formulation development and optimization, but would not be suitable for demonstration of human bioequivalence; larger species may be needed to evaluate relevant injection volumes (154).

Development of IVIVC can be particularly challenging for local delivery, such as ocular delivery, where it may be difficult or impossible to assess the local drug concentration in humans, and plasma levels may be extremely low and not indicative of local exposure. In animal models, local tissue exposure may be determined by sacrificing animals at specified timepoints and measuring tissue concentrations or drug content of explanted dosage forms, or by microdialysis methods (29,153,166).

#### **Manufacturing Process and Scalability**

Manufacturing processes for parenteral sustained-release formulations are often complex and many involve nonconventional unit operations. Considerations during process development include ensuring that stability and activity of the drug are not compromised, optimizing process yield and drug encapsulation (e.g., for microspheres), ensuring the release profile is reproducible within specified limits and, when relevant, that particle size is controlled to specifications (31). Scaling can be a challenge for many mixing operations; scalability can be improved by utilizing continuous processes, such as in-line mixing or extrusion (for implants). Solvent-based processes present additional environmental and safety challenges, such as the need for solvent-recovery handling, and ensuring residual solvent levels conform to specifications.

#### *Terminal Sterilization*

Ensuring sterility of parenteral sustained-release formulations is a significant challenge, given the dispersed nature of many of these systems, which often precludes sterile filtration. Sterile filtration may be feasible for systems formulated as solutions, such as oily-vehicle solutions and in-situ-forming depots dosed in organic solvents. Terminal heat sterilization may be possible for suspension formulations, and cloud point modifiers can be included to improve physical stability at high temperatures. This approach is not suitable for polymeric systems such as PLGA because of the relatively low  $T_g$  of the polymer (154).  $\gamma$ -Irradiation has been employed for terminal sterilization of PLGA microsphere and suspension systems, but the potential for polymer and drug degradation must be evaluated. As a result of these challenges, most parenteral sustained-release formulations are aseptically processed (154).

#### **Regulatory Considerations**

Depot delivery systems are subject to the same quality control requirements that govern other parenteral drug products, including sterility, pyrogen testing, drug content, impurities and degradates. The sterility test method used depends on the nature of the depot delivery system,

with the direct transfer method typically used for suspensions that cannot be solubilized in suitable solvents, and sterilized devices, and the membrane filtration method for other depot delivery systems (167). Although particulate matter testing is not required for suspensions, these systems can be dissolved in a suitable organic solvent to test for foreign particles (154). It is important to verify syringeability and injectability with appropriately-sized needles. While there is no regulatory guidance, viscosity measurements and evaluation of needle-clogging and plunger force can be used to assess these attributes. A fundamental understanding of release mechanisms and physicochemical changes within the delivery system is an important part of quality by design.

#### **Development Strategy and Economics**

The successful development and launch of parenteral sustained-release dosage forms can be a long and expensive process, owing to their high technical complexity, nonconventional unit operations, and long duration of action. It is critical to establish an early line of sight from the concept and compound properties to the market, to minimize additional cost and lost time. This involves establishing a target product profile early, including a thorough assessment of the market and target patient populations. It is important to ensure that the properties of the active are suitable for the desired sustained-release application, and that they are properly matched to the appropriate formulation approach. Ideally, if the need for sustained release is recognized early during discovery, compound potency and physicochemical properties, such as solubility and stability, should be designed to enable formulation using specified sustained-release technologies.

Sustained-release formulations are often developed as lifecycle management opportunities for compounds already in development or launched as conventional parenteral or oral formulations. As a result, there may be a significant body of existing safety and efficacy data in humans, and depot formulations typically do not enter clinical development until a thorough understanding of PK/PD and therapeutic window is available. In vitro release data and preclinical pharmacokinetic data should be used to design the dosage form to meet the target pharmacokinetic profile. As for any new formulation, preclinical safety studies must be run prior to initiation of clinical studies. Clinical dose ranging can be supported either by administering formulations with different release rates, or by administering different doses of a single formulation. It is desirable to initiate clinical studies with a formulation composition and manufacturing process that is representative of the intended commercial product to minimize the challenge of bridging formulation changes and process changes later in development. As this is rare in practice, and given a lack of regulatory bioequivalence guidelines for sustained-release dosage forms, formulation and process changes should ideally be supported by a validated IVIVC.

Development and product costs of sustained-release formulations are typically higher than conventional formulations because of their high technical complexity, long development timelines, nonconventional excipients and manufacturing unit operations, and higher doses of active per administration. This should be planned into the overall development strategy from the beginning.

#### **FUTURE DIRECTIONS**

The future of parenteral sustained delivery promises to be an exciting one, with the potential for significant advances that will meaningfully change the way medicines are administered. Technical advances will span from incremental improvements in existing technologies, to the introduction of new excipient materials, the development of systems that offer an improved level of control over drug release, and the emergence of new applications for depot delivery. This future will require pharmaceutical and formulation scientists to broaden their already multidisciplinary backgrounds even further into areas as diverse as microelectromechanical systems (MEMS), information sciences, and cell and tissue biology (168).

#### **Incremental Enhancements of Existing Technologies**

The pace of launching new parenteral sustained-release technologies over the last several decades has been relatively slow, due in part to the major challenges and costs inherent in